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Dated: December 15, 2016

PHYSICIAN PATIENT-SHARING NETWORKS AND PRESCRIPTION OF PSYCHOTROPIC POLYPHARMACY IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH MENTAL DISORDERS

By

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To the Faculty of the University of Houston, College of Pharmacy:

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Dedicated to my parents Arun Medhekar and Smita Medhekar

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EXECUTIVE SUMMARY

1. SPECIFIC AIMS

Psychiatric polypharmacy refers to the prescription of two or more psychiatric medications concurrently to a patient for the treatment of a single condition (Shrivastava, Kukreja, Kalra, & Shah, 2013). The major concerns associated with the use of polypharmacy include: risk of medication-related adverse events, complicated drug regimen affecting patient compliance, drug-drug interactions, cumulative toxicity, and patient morbidity and mortality (Maher, Hanlon, & Hajjar, 2013). According to the American Academy of Child and Adolescent Psychiatry "little data exists to support advantageous efficacy for drug combinations," and, "current clinical 'state-of-the-art' supports judicious use of combined medications, keeping such use to clearly justifiable clinical circumstances" (AACAP, 2001; Zonfrillo, Penn, & Leonard, 2005). Clinical guidelines recommend monotherapy as the preferred therapy in psychiatric practice. Despite these recommendations the use of psychiatric polypharmacy is quite common in clinical practice with the overall prevalence ranging from 13%-90% (Chen, Patel, Sherer, & Aparasu, 2011).

Due to the growing concerns of polypharmacy and off-label use of psychotropic medications in children and adolescents, 42 states of the United States have developed programs to manage/monitor the appropriate use of psychotropic medications (CMS, 2014). The Texas child welfare system released a "best practices" guide to ensure appropriate use of psychotropic medications for children in foster care in February 2005 which was updated in 2007, 2010 and 2013 (DFPS, 2016). In 2014, the Texas Health and Human Services Commission modified Section 8.1.21.6 of its Uniform Managed Care Terms and Conditions and made the Psychotropic Medication Utilization Review (PMUR) a mandatory process for Medicaid Managed Care

Organizations (MCOs). The PMUR involves monitoring of "guideline non-concordant" prescribing of psychotropic medications in children, specifically focusing on the use of psychotropic polypharmacy (Psychotropic Medication Utilization Parameters, 2016).

The existing PMUR process views guideline non-concordant prescribing as the outcome of individual providers' knowledge and attitude. Once a provider with frequent guideline non-concordant prescribing is identified, he/she is referred to further investigation conducted by medical professionals from the health plan and if warranted disciplinary action including termination from the network may be implemented (DFPS, 2016). However, these investigations do not consider the effect of the environment from which such behavior originated. Additionally, though these review procedures are effective in changing physicians' prescribing behavior, they are resource intensive. The review committees of most MCOs only have the capacity to review and reach out to a small fraction among thousands of contracted providers. Further, the individual focused PMUR fails to acknowledge that some guideline non-concordant uses, especially polypharmacy could arise from poor communication among providers rather than due to the individual's prescribing behavior.

Physicians are not isolated individuals but part of a social structure who may be influenced. Past studies have shown that the physicians' prescribing behavior can be influenced by peers in addition to their own personal preferences. If there is a strong peer effect in the prescribing of psychotropic medications to children, targeting and changing the prescribing behavior of guideline non-concordant prescribers could lead to a cascading effect in guideline diffusion among other physicians within the network, resulting in increased concordance with guidelines. Social Network Analysis (SNA) is a set of theories and techniques used to understand how social relationships (e.g., friendship, advice seeking, and reputation) influence behaviors

(Gesell, Barkin, & Valente, 2013; Valente, 2010; Valente, Gallaher, & Mouttapa, 2004). SNA examines physicians' behaviors in the context of their professional social structure (network) where they communicate, collaborate, compete and exert influences on each other. SNA provides a unique perspective to understand the underlying reasons of prescribing decisions and medication errors. It has the potential to address limitations of the existing PMUR program and to improve the quality of treatment for Medicaid enrolled children with mental disorders. Therefore, the objective of the proposed research is to examine the role of inter-provider relationships (communication, collaboration and peer influence) in guideline-non-concordant use of psychotropic medications. The specific aims of the research are:

Aim I: To advance the understanding of the prevalence of and risk factors associated with long-term multiclass psychotropic polypharmacy among children and adolescents with mental/behavioral disorders in a Texas Medicaid population.

Aim II: Among children with mental/behavioral disorders who were prescribed psychotropic medications by multiple prescribers, to examine the relationship between care-density (patients' care team cohesiveness) and receipt of psychotropic polypharmacy

Hypothesis I: *Patients with higher care-density (stronger care team cohesiveness) will have less likelihood of receiving multiclass psychotropic polypharmacy.*

Aim III: Among children with MHD who were prescribed psychotropic medications by single prescriber, to examine the effect of physician peer-influence on the prescribing of psychotropic polypharmacy.

Hypothesis II: *The likelihood of prescribing psychotropic polypharmacy is affected by physician peer-influence based on both direct communication (affiliation exposure) and*

comparison between peers who occupy similar network positions (structural equivalence exposure).

2. BACKGROUND AND SIGNIFICANCE

2.1 Background

Definition of psychotropic polypharmacy:

Polypharmacy is defined as the practice of prescribing or administering multiple medications concurrently in a single patient for the treatment of a single condition. The definition is solely based on the number of medications prescribed and does not take into account the clinical relevance or the adequacy of the proposed therapeutic regimen. The term polypharmacy suggests the use of more medications than is 'clinically indicated' (Shrivastava, Kukreja, Kalra, & Shah, 2013). Psychiatric polypharmacy is the practice of polypharmacy in psychiatric therapy. The most commonly used definition of psychiatric polypharmacy is the use of two or more psychiatric medications in the same patient, or the use of two or more psychiatric medications (of same chemical class or same pharmacological action) to treat the same condition (Shrivastava, Kukreja, Kalra, & Shah, 2013; NASMHPD, 2001).

Short-term psychotropic polypharmacy:

Despite the scarcity of evidence for or against the use of polypharmacy, there are instances where short-term polypharmacy is clearly appropriate or even necessary. The primary reason for prescribing more than one psychotropic agent for an extended period of time is when a single medication is not effective. However, before initiating on multiple psychotropic agents the patient should first receive adequate trials on a number of single medications as the clinical effect of the medication may not be seen until weeks. Usually, most medications require at least 5 half-lives to reach a consistent concentration in the body. A valid trial period to determine the

effectiveness of a psychiatric medication is at least 21 days of continuous use on the same dose. Other situation when multiple psychotropic agents may be appropriate for short-term use is while changing a patient from one psychotropic agent to another. Usually clinicians intentionally either overlap or cross-titrate the two medications which results in a brief period of combination treatment. The old medication is concurrently used with the new until the new medication shows the desired effect. It is extremely important to avoid the 'crossover trap' in such situations where the patient shows clinical response before completion of the crossover and both medications are continued indefinitely (Disability Rights California, 2004; NASMHPD, 2001).

General concerns of long-term psychotropic polypharmacy:

Preskorn and Lacey (2007) listed a few conditions under which polypharmacy is justified: i) to treat two pathophysiologically distinct but comorbid disorders, ii) to treat an adverse effect produced by the primary drug, iii) to provide acute amelioration while awaiting the effect of another medication, iv) to treat intervening phases of an illness and v) as an adjunct to boost the efficacy of primary treatment and treat exacerbations of the illness (Preskorn & Lacey, 2007). In each of these circumstances, the combinations are used only to achieve the short-term goals as long-term use of polypharmacy often results in increased risk of adverse drug events (ADEs), drug-interactions, medication non-adherence, patient morbidity and mortality, and is highly likely to increase overall drug expenditures (Fontanella, Warner, Phillips, Bridge, & Campo, 2014; Khan & Preskorn, 2005; Maher, Hanlon, & Hajjar, 2013). Evidence based research and expert opinion caution clinicians about the risk associated with the use of polypharmacy.

Adverse drug events: Taking several drugs contributes to the risk of having an ADE. In a population based study, patients taking ≥ 5 medications had an 88% increased risk of

experiencing an ADE compared to those who were taking fewer medications (Bourgeois, Shannon, Valim, & Mandl, 2010). In another study of nursing home residents, the rates of ADEs were twice as high as in patients taking ≥ 9 medications compared to those taking less number of medications (Nguyen, Fouts, Kotabe, & Lo, 2006). A study among veterans found that patients taking ≥ 5 medications were 4 times more likely to be hospitalized from an ADE (Marcum et al., 2011). Another study in outpatient practices among elderly patients found that taking six or more medications increased the risk of adverse drug events by fourfold (Pretorius, Gataric, Swedlund, & Miller, 2013). The concurrent use of medications can amplify individual drug's side effects. When used in combination two medications with mild sedative effects can cause significant sedation (Kramer, 2000). Similarly, concurrent use of drugs that cause mild weight gain may cause severe weight gain (Hashimoto et al., 2012; Kramer, 2000). Compared to monotherapy, antipsychotic polypharmacy is found to be associated with an increased risk of having pre-metabolic syndrome, even after adjusting for patients' lifestyle characteristics (Misawa et al., 2011). It has been demonstrated that young age and polypharmacy have positive associations with an increased risk of obesity and cardiovascular, cerebrovascular or hypertensive adverse events (De Hert, Detraux, Winkel, Yu, & Correll, 2011).

Drug-drug interactions: Combination of drugs may lead to pharmacokinetic and pharmacodynamic interactions in the body as presence of one drug might alter the nature, magnitude and the duration of effect of the other drug (Werder & Preskorn, 2003). The absorption, distribution, metabolism and excretion of one drug might be altered by the other drug thereby changing the blood levels of the other drug. In a prospective cohort study of hospitalized adults taking 5 or more medications, the prevalence of drug-drug interaction was 80%. The probability of the drug interactions increased with the number of medications, patients taking 5-

20 medications had a 50%-100% probability of interaction (Doan, Zakrzewski-Jakubiak, Roy, Turgeon, & Tannenbaum, 2013; Maher, Hanlon, & Hajjar, 2013). Use of certain antipsychotics in combination with anticholinergic drugs may increase the anticholinergic effects of both drugs leading to confusion, dehydration, constipation, or development of fatal cholinergic crisis (Disability Rights California, 2004). A brief list of possible drug-drug interactions associated with psychotropic medications is listed in Table 1 (Sengul et al., 2014).

Table 1: Interaction risk among drugs and associated outcome

Outcome of interaction risk	Interacting drugs
QT prolongation	a) citalopram with quetiapine /fluphenazine/ paliperidone /risperidone /pimozide /haloperidol b) ziprasidone with risperidone /quetiapine/ pimozide/ chlorpromazine c) quetiapine with lithium/ fluphenazine/ haloperidol/ pimozide d) clozapine with risperidone/ quetiapine/ haloperidol /aripiprazole /fluphenazine e) haloperidol with lithium/ chlorpromazine/ fluphenazine
Change in Drug levels	a) quetiapine-CBZ interaction b) VAL–risperidone, VAL-TCA interaction c) CBZ with risperidone/aripiprazole/fluoxetine/ d) sertraline/paroxetine/fluoxetine/citalopram/escitalopram with risperidone/aripiprazole/clozapine interaction e) lamotrigine and clozapine/ olanzapine/ risperidone interaction
Hepatotoxicity	Olanzapine and VAL interaction
Bradycardia-hypertension	a) All interactions between benzodiazepines and olanzapine or clozapine b) All propranolol and biperidene/ quetiapine/ lithium or olanzapine interaction

Non-adherence: Non-adherence with drugs in adults has been associated with the complicated drug regimens and polypharmacy (Hajjar, Cafiero, & Hanlon, 2007; Vik, Maxwell, & Hogan, 2004; Lee et al., 2013; Salazar, Poon, & Nair, 2007). One of the main causes of medication non-compliance as stated by patients is the complexity of drug regimen (Jimmy & Jose, 2011). Corsonello et al. (2009) suggested that patients are often confused by the drug regimen (Corsonello, 2009). Fulmer et al (2001) reported that older adults usually take as many as 5-10

medications daily leading to confusion about which medications to take when (Fulmer, Kim, Montgomery, & Lyder, 2001). In a systematic review by Rollason et al. (2003) it was found that among patients taking 4 or more medications the rate of patient non-adherence was as high as 35% (Rollason & Vogt, 2003). In another study by Rottlaender et al. (2007), it was found that polypharmacy with more than four pills a day significantly decreased medication compliance (Rottlaender, Scherner, Schneider, & Erdmann, 2007).

Increased healthcare costs: Polypharmacy significantly contributes to healthcare costs both to the patient and the healthcare system. A retrospective cohort study found that polypharmacy was associated with a 30% increase in total medical costs (Akazawa, Imai, Igarashi, & Tsutani, 2010). Another study conducted in Sweden reported that those taking 5 or more medications had a 6.2% increase in prescription drug expenditure and those taking 10 or more medications had a 7.3% increase in prescription drug expenditure (Hovstadius & Petersson, 2013). Health plans are at high risk for significant costs associated not only with increased drug utilization patterns due to polypharmacy but also are at risk of costs associated with the potential health complications due to mixing many medications (Marabella, 2015).

Morbidity and mortality: The risk of drug toxicity or overmedication increases with use of multiple medications at high dosages. Not only do sicker patients get multiple medications, they usually get them at higher doses (Rosack, 2003). It has been found that antipsychotic polypharmacy results in patients being prescribed higher doses of antipsychotic medication (Lelliott et al., 2002). Further, the likelihood of death is directly proportional to the number of medications a person with a psychiatric disability is taking, even when controlled for underlying diseases (NASMHPD, 2001; Werder & Preskorn, 2003). Increased risk of mortality has been observed in patients with schizophrenia with the use of more than one antipsychotic medication

concurrently (Waddington, Youssef, & Kinsella, 1998; Maher, Hanlon, & Hajjar, 2013; NASMHPD, 2001).

Furthermore, polypharmacy has been known to lead to other negative consequences like cumulative toxicity, medication errors, impairment of functional status, and cognitive impairment.

Further concerns of long-term pediatric psychotropic polypharmacy:

Research has consistently shown an increase in the number of children prescribed various classes and combination of psychotropic medications (Pidano, Meyers, & Honigfeld, 2011; Naylor et al., 2007; Martin, Van Hoof, Stubbe, Sherwin, & Scahill, 2003; Zito, 2000). The use of psychiatric polypharmacy in children has been on the rise during the past decade. This is alarming because not only are the children at high risk of the potential negative consequences associated with polypharmacy as discussed in the previous section but also there is limited scientific evidence for understanding the immediate or long-term effects of polypharmacy on a child's growth and development. Many of the medications used in pediatric population have not been studied or approved for use with children (Magellan Health, 2013). Often these medications are prescribed "off-label", meaning for a mental disorder or age group apart from the one for which they have been approved by the Food and Drug Administration (FDA). Drugs are usually tested in isolation against placebo or suitable comparator, so enough data is not available on which drug combinations may be harmful. Further these clinical trials are usually conducted in adult population and exclude children and adolescents, thus overall pediatric clinical evidence is hard to come by. Among all the concerns in children and adolescents regarding polypharmacy the most crucial is that of increased risk of adverse events (Zonfrillo, Penn, & Leonard, 2005). Numerous examples of drug-drug interactions have come forward in this population. For

example, concurrent use of methylphenidate and clonidine has led to sudden death of 4 children. Death of a 9 year old on fluoxetine, promethazine, methylphenidate and clonidine due to overdose has been reported (Cantwell, Swanson, & Connor, 1997; Popper, 1995; FDA, 2010). Serotonin syndrome leading to high levels of serotonin accumulation in the body can result when a youth receives two or more medications with serotonergic properties. Further, the safety of some monotherapy has been questioned, example antipsychotics have been found to cause weight gain and metabolic disorders in children and use of anti-depressants has resulted in development of suicidal ideation in some children. Thus if monotherapy can cause such harm it certainly raises questions regarding safety of polypharmacy in children.

Ever widening gap between guidelines and practice:

According to the American Academy of Child and Adolescent Psychiatry (AACAP) "little data exists to support advantageous efficacy for drug combinations," and, "current clinical 'state-of-the-art' supports judicious use of combined medications, keeping such use to clearly justifiable clinical circumstances" (AACAP, 2001; Zonfrillo, Penn, & Leonard, 2005). Currently, only a few psychiatric drugs are approved by the US Food and Drug Administration for use in children, all other usage of psychiatric medications in children is off-label. Clinical guidelines recommend monotherapy as the preferred therapy in psychiatric practice.

Despite these recommendations the use of psychiatric polypharmacy is quite common in clinical practice. The overall prevalence of psychiatric polypharmacy varies between 13-90% depending on the clinical setting and study design (Taylor, 2002; De las Cuevas & Sanz, 2004; Stahl, 2002). Up to 33% of patients visiting outpatient psychiatry department have been found to be on three or more psychotropic medications (Mojtabai & Olfson, 2010; Shrivastava, Kukreja, Kalra, & Shah, 2013). A significant decline in the use of psychotropic monotherapy and increase in use of

polypharmacy has been observed in the inpatient setting during the last few decades. A review by Rittmannsberger et al (2002) reported the use of monotherapy in 48% patients before 1980, which declined to 31% between the years 1981-1990 and further declined to 20% in 1991-2000 (Rittmannsberger, 2002). A study from NIMH shows that prescription of 3 or more medications at discharge increased from 5% in 1974 to 40% in 1995 (Presborn & Flockhart, 2006). Psychiatric polypharmacy is not only widespread in adult population, but also increasingly seen in children and adolescents. The prevalence of psychotropic polypharmacy has increased by two to seven folds in this population. Overall, the estimated prevalence of psychiatric polypharmacy ranged from about 14% among children insured by Medicaid to about 73% among children in foster care. In the study by Zito et al among the children in Texas foster care the prevalence of multiclass psychotropic medication use was found to be as high as 72.5% (Zito et al., 2008). Prevalence estimates and definitions of psychotropic polypharmacy vary with study design and population. Table 2 summarizes the prevalence of psychotropic polypharmacy in pediatric non-foster population.

Table 2: A summary of prevalence of psychotropic polypharmacy in the United States pediatric population

Study	**Population**	**Definition of polypharmacy**	**Prevalence**
Pediatric Non-Foster Population			
Chen, Patel, Sherer, & Aparasu, 2011	Medicaid population: California, Illinois, New York and Texas, children age 6-18 years of age	≥ 2 psychotropic medications from the same or different categories, receiving ≥14, ≥30, ≥60, and ≥90 consecutive days of overlapping prescription fills	≥ 14 days: 28.8% ≥ 30 days: 27.2% ≥ 60 days: 20.9% ≥ 90 days: 17.7%
Comer, Olfson, & Mojtabai, 2010	National Ambulatory Medical Care Surveys (children and adolescents) 1996-2007 (N=3466)	Multiclass psychotropic treatment during a physician office visit	19%

McIntyre & Jerrell, 2009	South Carolina Medicaid , children and adolescents with major depression from 1996-2005 (N=1544)	Physician who prescribed ≥ 2 psychotropic medications	1996: 6.7% 2005:41.6%
Duffy et al., 2005	Cross-sectional data reported for youths ages 2–17 by the American Psychiatric Practice Research Network of psychiatric patients and treatment for 1997–1999 (N=392)	Concurrent use of ≥ 2 psychotropic medications	52%
DosReis et al., 2005	Youth age < 20 years enrolled in Medicaid or SCHIP in 2 states in 1999 (N=40856 and N=235093)	Use of ≥ 2 psychotropic medication classes within same month	28%-30%
Martin, Van Hoof, Stubbe, Sherwin, & Scahill, 2003	Children and adolescents ranging in age from newborn to 18 years enrolled in Connecticut Medicaid managed care for 1998-1999 (N=196549)	Claims for medications from ≥ 2 psychotropic drug classes during 7-day interval after index prescription	13.6%
Olfson, Marcus, Weissman, & Jensen, 2002	U.S. civilian, noninstitutionalized population NMES 1987 and MEPS 1996	Use of ≥ 2 psychotropic medication classes during 1 year period	1987: 3% 1996: 23%
Rappley et al., 2002	Pharmacy claims data (< 3 years age), ADHD patients Michigan Medicaid 1995-1996	Use of ≥ 2 psychotropic medications filled on the same day, or within 7 days of each other over the 15 months	35%
Bhatara, Feil, Hoagwood, Vitiello, & Zima, 2002	National Ambulatory Medical Care Surveys (children <18 years of age) 1993-1998	% visits with concomitant psychotropic prescription	1993-94: 4.78% 1995-96: 10.79% 1997-98: 24.70%

Pediatric Psychotropic Polypharmacy and Medicaid Psychotropic Drug Utilization Review

Due to the growing concerns of potential inappropriate use of psychotropic medications in children and adolescents a number of measures have been implemented by State Medicaid agencies with the help of CMS (Centre for Medicare and Medicaid Services). Medicaid Drug Utilization Review (DUR) programs have been employed by each of the 50 states, which employ

a variety of techniques to intensify the oversight of prescribing of the psychotropic medications in children, especially for children in foster care (Medicaid and CHIP Payment and Access Commission, 2015). According to the Medicaid Drug Utilization Review Comparison/ Summary Report of 2014, forty-one states (82%) have programs in place to either manage or monitor the appropriate use of psychotropic medications in children. Thirty-six states have programs that monitor all children, not just the children in foster care. In general, every state has pre-programmed edits to screen the appropriate use of psychotropic medications in children, a few examples of such targeted edits are: preauthorization edits for younger children <5 years of age which requires a manual review of prescription request by a panel of experts; therapeutic duplication edits to avoid duplication of medications from the same therapeutic class or with same pharmacological action; preauthorization edits to reduce the rates of polypharmacy and specific edits for prescribing and monitoring guidelines for use of psychotropic medications in the children in foster care. A few states also have data registries that analyze the prescribing of psychotropic drugs and provide physician feedback and training (CMS, 2014).

The Effect of Medicaid Psychotropic Drug Utilization Review on Pediatric Psychotropic Polypharmacy

At least 36 states have implemented programmed edits to manage or monitor the use of psychotropic polypharmacy and off-label use of psychotropic medications in children and adolescents in foster Care. The STAR Health Psychotropic Medication Utilization Review (PMUR) implemented by the state of Texas is one such program. The Texas child welfare system released a “best practices” guide to ensure appropriate use of psychotropic medications for children in foster care in February 2005. These quality metrics have been updated in 2007,

2010 and 2013 (DFPS, 2016). In 2014, the Texas Health & Human Services Commission (HHSC) modified Section 8.1.21.6 of its Uniform Managed Care Terms & Conditions and made the PMUR a mandatory process for Medicaid Managed Care Organizations (MCOs). The PMUR involves monitoring of "guideline non-concordant" prescribing of psychotropic medications in children, specifically focusing on the use of psychotropic polypharmacy (Psychotropic Medication Utilization Parameters, 2016). Since the introduction of "best practices" in 2005 and the later updates in PMUR, the prescribing of psychotropic medications in the foster care population has been on a downward trend. Based on the available data, the percentage of foster children receiving any psychotropic medications for ≥ 60 days peaked in 2004 at 29.9% and at the end of year 2009 had dropped to 19.7%. The rate of children in foster care who experienced class polypharmacy has dropped by nearly 75%, and the percentage receiving 5 or more psychoactive medications is down by nearly 80% (Texas Health and Human Services Commission, 2010). This reduction in the rate of prescribing psychotropic medications and psychotropic polypharmacy is largely attributable to the use of PMUR.

The need to further address inappropriate use associated with psychotropic polypharmacy and the limitations of Medicaid psychotropic Drug Utilization review

There are a number of limitations to the current Medicaid Drug Utilization review parameters. First of all, these parameters are only used to monitor guideline non-concordant prescribing which result from individual providers' knowledge and attitudes. The whole emphases of these parameters are on the non-concordant behavior of a single individual provider. In these settings once the individual provider who is frequently involved in out-of-parameter prescribing has been identified, peer-to peer interview is conducted reasoning such behavior and

corrective action is taken to avoid future repetition (DFPS, 2016). In this approach, the out-of-parameter prescribing behaviors are handled one by one, and there is no investigation or modification of the environment from which the behavior originated. These DURs and intervention programs fail to acknowledge that some out-of-parameter uses, especially therapeutic duplication and polypharmacy, could arise from poor communication among providers rather than due to the individual's out-of-parameter practice. Second, due to the complexity of disorders among children and adolescents, they usually see multiple providers as compared to their peers. As a result they may have medications prescribed from several sources which can lead to therapeutic duplication and polypharmacy. Third, the current parameters do not take in to consideration the effect of peer influence. Past studies have shown that the physicians' prescribing behavior can be influenced by his/her peers in addition to their own personal preferences. Lastly, there is a lot of variation in the parameters specifically with respect to the definition of duration of psychotropic polypharmacy. Some parameters define polypharmacy on the basis of use of multiple psychotropic medications for more than 60 days while others define it based on use of multiple psychotropic medications for more than 90 days (PSYKES, 2011; Psychotropic Medication Utilization Parameters, 2016).

The potential barriers of expanding PMUR from foster children to all Medicaid covered Pediatric Population

Although the PMUR parameters are specifically targeted for the foster care population, there is some overlap between the physicians treating the children in foster care and those treating the general Medicaid children. So there is a potential possibility that these parameters are also being implemented in the psychiatric care of the general Medicaid children. However,

there are certain barriers in the expansion of PMUR from foster care to the general Medicaid population. About 80% of the Texas Medicaid population is enrolled in Medicaid managed care as of August 2014. Within Medicaid managed care in Texas there currently are three comprehensive programs: STAR (low-income families, children, pregnant women, and some former foster care youth), STAR+PLUS (mostly adults 21 years and older), and STAR Health (Foster Care). Of these only the STAR health program monitors use of psychotropic medications using the PMUR medication utilization parameters (Texas Health and Human Services Commission, 2015). STAR Health forms a very small share (only 0.8%) of the total Medicaid population. There are children who do not qualify for STAR Health and whose psychotropic medication usage is not monitored in the system. These include the children who are placed in Texas through an Interstate Compact on the Placement of Children (ICPC), children who are dual eligible for Medicaid and Medicare, and general Medicaid children population (Barillas, 2009).

The STAR Health program is the most comprehensive managed care plan under Texas Medicaid. The population enrolled in STAR Health is considered as a high-risk population with greater medical and behavioral needs than most children in Medicaid. STAR Health clients receive medical, dental, vision, and behavioral health benefits, including unlimited prescriptions. The program includes access to an electronic health record called the Health Passport, which contains a history of each child's demographics, doctor visits, immunizations, prescriptions, and other pertinent health-related information. The program also includes a 7-days-per-week, 24-hours-per-day nurse hotline for caregivers and DFPS caseworkers. Use of psychotropic medications is carefully monitored in this population. STAR health has a large Human resource in terms of caseworkers and caregivers who help in the coordination of care delivered; facilitation of

communication between providers; set up follow up appointments and implementation of plan of care. They further help with easy outreach to the providers involved in the provision of healthcare to the enrolled children. The resources invested in STAR Health are more than that in any of the other plan in the Texas Medicaid managed care (Texas Health and Human Services Commission, 2015). The lack of resources in other managed care programs become a potential barrier for the implementation PMUR to all Medicaid covered pediatric population. The paucity of funding and manpower leads to more difficulty in outreaching the providers involved in provision of care. The medical affairs of most MCOs rely on a few physicians and pharmacists to manage all diseases and treatments covered by the plan. They only have the capacity to review and reach out to a small fraction among thousands of contracted providers. Not every MCO has the financial and human resource available to conduct this review process.

Physicians Social Network and Prescribing behavior

Physicians are not isolated individuals but part of a social structure who may be influenced. It is seen that clusters of physicians usually adopt the behavior of their peers and opinion leaders (most influential physician). This influence is exerted due to a variety of reasons including day-to-day interactions, referrals, and shared patients (Gallo, 2012). If there is a strong peer effect in the prescribing of psychotropic medications to children, targeting and changing the prescribing behavior of guideline non-concordant prescribers could lead to a cascading effect in guideline diffusion among other physicians within the network, resulting in increased concordance with guidelines. Furthermore, due to complexity of mental disorders, patients usually see multiple providers. Thus, poor communication and collaboration among the patients' care team can lead to multiple prescriptions of same class of medications (polypharmacy).

Efficient channels of communication and collaboration among physicians are recognized as a catalyst to improved patient care (Uddin, Hossain, Hamra, & Alam, 2013). It allows input from multiple providers caring for the same patient, which produces decisions based on complete information, which in turn lead to better patient outcomes.

Social Network Analysis (SNA) is a set of theories and techniques used to understand how social relationships (e.g., friends/peers, advice seeking, and reputation) influence behaviors (Gesell, Barkin, & Valente, 2013). SNA is commonly used to study relationships between individuals and communities as they interact with each other (Valente, Gallaher, & Mouttapa, 2004). In the healthcare domain, social network analysis has been used in different settings, for example to study collaboration among healthcare professionals in specific healthcare environments, to understand the impact of team structure on quality of care. Studies have been conducted using SNA to analyze health care networks, addressing topics such as the exchange of clinical advice, the diffusion of pharmaceutical use, or organizational performance and cost-efficiency (Keating, Ayanian, Cleary, & Marsden, 2007; Christakis & Fowler, 2010; Iyengar, Van den Bulte, & Valente, 2011; Barnett et al., 2012). The studies on diffusion of new pharmaceuticals have used SNA to analyze the influence of opinion leaders or key action leaders on daily prescribing practices (Iyengar, Van den Bulte, Eichert, & West, 2011). Social network analysis has been used to study the effect of patient sharing networks on quality of care, cost of care, hospital outcomes (Mundt et al., 2015; Pollack, Weissman, Lemke, Hussey, & Weiner, 2012; Uddin, Hossain, Hamra, & Alam, 2013). Lately a few studies have also used Social network analysis to study the effect of patient sharing networks on multiple-provider prescribing of drugs and for examination of prescribing error rates (Creswick & Westbrook, 2015; Ong et al., 2015).

SNA examines physicians' behaviors in the context of their professional social structure (network) where they communicate, collaborate, compete and exert influences on each other. The measures of SNA that will be used in the current study include cohesion, structural equivalence and care-density. The two contagion mechanisms, cohesion (direct communication) and structural equivalence (comparison) will be used to study peer influence. Cohesion refers to the actors (physicians) being directly connected in a network. In the healthcare context, cohesion implies that physicians acquire information about their peers behavior or attitudes through direct communication. On the other hand the peer influence through structural equivalence is based in part on the competition that exists between people when they evaluate new situations. Burt and others (Burt, 1987; 2010; Fujimoto & Valente, 2012) have reported that "the more similar ego's and alter's relations with other persons- the more that alter could substitute for ego in ego's role relations, and so the more intense ego's feeling of competition with the alter, the more likely that ego will quickly adopt any innovation". Further, the effect of patients' care team interactions will be studied using the care-density measure. Care-density corresponds to the care team's cohesiveness which is theoretically a representation of effective collaboration and communication between the patient's care teams (Pollack, Weissman, Lemke, Hussey, & Weiner, 2012; Pollack, Lemke, Roberts, & Weiner, 2015).

SNA provides a unique perspective to understand the underlying reasons of prescribing decisions and medication errors. Therefore, in this study we use measures of Social Network Analysis to examine the role of inter-provider relationships (communication, collaboration and peer influence) in guideline-non-concordant use of psychotropic medications.

2.2 Rationale and Significance

Psychotropic polypharmacy refers to the prescription or administration of a) two or more medications to treat the same mental health condition or b) two or more psychotropic medications of the same drug class. Psychotropic polypharmacy is a high priority quality concern especially in children and adolescents as there are only a limited number of clinical trials evaluating the effectiveness, risks and long-term effects of using two or more psychiatric drugs in combination. The major concerns associated with the use of polypharmacy include: adverse drug reactions, drug-drug interactions, cumulative toxicity, medication errors, patient non-compliance and patient morbidity and mortality (Kingsbury, Yi, & Simpson, 2001; NASMHPD, 2001; Werder & Preskorn, 2003). Despite the risks and concerns, there is an increase in the trend of psychotropic polypharmacy in children and adolescents. In a national study of office-based psychotropic prescription in children and adolescents with a psychiatric diagnosis, the rate of polypharmacy increased from 22% to 32% over 12 years. In a recent study of Medicaid claims in one state, 38% of youth on any psychotropic medication were prescribed more than one drug.

As a result of the growing concerns of psychotropic polypharmacy in children and adolescents the State Medicaid agencies with the help of CMS employed Drug Utilization Review programs in all the 50 states, which employ a number of measures to intensify the oversight of prescribing of the psychotropic medications in this population. Psychotropic Medication Utilization Review (PMUR) for children in foster care is one such measure developed by the Texas HHSC, which involves monitoring of "guideline non-concordant" prescribing of psychotropic medications in children, specifically focusing on the use of psychotropic polypharmacy. Although these guidelines and utilization review system is specifically targeted for the foster care population, there is some overlap between the physicians

treating the children in foster care and those treating the general Medicaid children. So it is highly likely that these parameters are also being implemented in the psychiatric care of the general Medicaid children. Many managed care organizations (MCOs) have also started implementing criteria similar to PMUR for monitoring appropriate use of psychotropic medications in children.

However, there are a number of limitations to these psychotropic medication utilization parameters. First of all, these parameters are only used to monitor guideline non-concordant prescribing which result from individual providers' knowledge and attitudes. These DURs and intervention programs fail to acknowledge that some out-of-parameter uses, especially polypharmacy, could arise from poor communication among providers rather than due to the individual's out-of-parameter practice. Second, due to the complexity of disorders among children and adolescents, they usually see multiple providers as compared to their peers. As a result they may have medications prescribed from several sources, which can lead to therapeutic duplication and polypharmacy. Third, the current parameters do not take in to consideration the effect of peer influence. Past studies have shown that the physicians' prescribing behavior can be influenced by his/her peers in addition to their own personal preferences.

Physicians seldom practice as isolated individuals; they are a part of a social structure that involves clusters of physicians treating a certain set of patients over a period of time. It is seen that these clusters of physicians usually adopt the behavior of their peers. They can be influenced by their peers due to a variety of reasons including day-to-day interactions, referrals, and shared patients. If there is a strong peer effect in the prescribing of psychotropic medications to children, targeting and changing the prescribing behavior of guideline non-concordant prescribers could lead to a cascading effect in guideline diffusion among other physicians within

the network, resulting in increased concordance with guidelines. Furthermore, patients with mental disorders usually visit multiple providers. Poor communication and collaboration among these providers can lead to multiple prescriptions of same class of medications (polypharmacy).

Social Network Analysis (SNA) is a set of theories and techniques used to understand how social relationships influence behaviors. SNA examines physicians' behaviors in the context of their professional social structure (network) where they communicate, collaborate, compete and exert influences on each other. SNA provides a unique perspective to understand the underlying reasons of prescribing decisions and medication errors. It has the potential to address limitations of the existing PMUR program and to improve the quality of treatment for Medicaid enrolled children with mental disorders. Therefore, the objective of the proposed research is to examine the role of inter-provider relationships (communication, collaboration and peer influence) in guideline-non-concordant use of psychotropic medications using measures of social network analysis. The current study would inform the feasibility of designing and implementing social network theory guided interventions to accelerate guideline diffusion and reduce inappropriate use due to poor communication among physicians.

2.3 Innovation

The current study uses the Texas Psychotropic Medication Utilization Review (PMUR) guidelines and the measures of Social Network Analysis to study the use of psychotropic polypharmacy (guideline non-concordant use) in children and adolescents enrolled in the Texas Children's Health Plan (TCHP). The TCHP is a unique Health Maintenance Organization (HMO) created just for children. TCHP is an administrator for the State Children's Health

Insurance Program (CHIP) and STAR/Medicaid managed care programs making TCHP the best source of data to study the implementation of the PMUR guidelines.

Previous studies on psychotropic polypharmacy are mostly cross-sectional evaluations on prescribing of psychotropic medications at a single point of time and often have not considered the overlapping period of concurrent use while defining psychotropic polypharmacy. Some longitudinal studies that have taken into consideration the duration of overlap have inconsistent definitions for the period of overlap. None of these studies have used the State mandated Medicaid drug utilization review guidelines for defining psychotropic polypharmacy. The current study uses the PMUR parameters developed by HHSC for the children in Texas foster care to define the "guideline non-concordant" use of psychotropic medications, specifically focusing on psychotropic polypharmacy.

Further, the current PMUR guidelines emphasize solely on the non-concordant behavior of a single individual provider for review of potential inappropriate use and do not take in to consideration the role of inter-provider relationships (communication, collaboration and peer influence) on such non-concordant behavior. Past studies have shown that physicians' peers and opinion leaders can influence prescribing decisions. Also, involvement of multiple physicians in the provision of care can lead to therapeutic duplication due to poor communication and collaboration between physicians. In view of these limitations the current study proposes to use the theories and techniques of Social Network Analysis to understand how peer-influence, communication and collaboration between physicians affects the adoption of the guidelines. SNA will help understand the underlying reasons of prescribing decisions. Social Network analysis has been used previously to study the effect of patient sharing networks on prescribing practices and diffusion of new pharmaceuticals. However, none of these studies have used SNA

to study the effect of patient sharing networks on use of psychotropic polypharmacy (guideline non-concordant use).

To our knowledge this is the first study to use Social Network Analysis to understand the role of inter provider relationships in guideline non-concordant use of psychotropic medications.

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The next three sections provide details on the methods, study design, results, and conclusions in the form of manuscript drafts for each of the specific aims

Manuscript 1: Specific Aim 1

Manuscript 2: Specific Aim 2

Manuscript 3: Specific Aim 3

MANUSCRIPT 1

Psychotropic Polypharmacy in the Treatment of Children and Adolescents with Mental Disorders: Prevalence and Risk Factors

Abstract

BACKGROUND: Psychotropic polypharmacy (PP) is highly prevalent in the treatment of pediatric mental disorders. However, literature studying the risk factors associated with use of PP is scarce, especially with respect to whether risk factors differ between patients treated by single prescriber (SP) versus multiple prescribers (MP).

OBJECTIVE: To advance the understanding of the prevalence of and risk factors associated with long-term multiclass psychotropic polypharmacy (PP) among children and adolescents with mental/behavioral disorders in a Texas Medicaid population.

METHODS: A retrospective cross-sectional study was conducted using the 2013-2015 administrative claims data from a Medicaid Managed Care Organization (Texas Children's Health Plan). The study included individuals: a) ≤18 years of age, b) diagnosed with a mental disorder, and c) had at least one pharmacy claim of psychotropic medication during the study period. Based on the number of prescribers involved in the treatment the individuals were categorized into two groups: a) single prescriber (SP) and b) multiple prescribers (MP). PP was defined as the receipt of ≥ 2 psychotropic medications from different drug classes concurrently for 60 days or more. Two separate logistic regression models (SP and MP) were conducted to determine associations between PP and patients demographics, diagnosis, clinical complexity and prescriber characteristics. The Farilie decomposition method (extension of Blinder-Oaxaca [BO] decomposition) was further applied to test the differences in receipt of psychotropic polypharmacy between patients treated by PCPs vs those treated by specialists

RESULTS: A total of 24,147 children and adolescents met the inclusion criteria. The prevalence of multiclass PP was 20.09%. Other significant factors associated with PP were patient race and diagnosis of bipolar disorders and depression, as well as the number of mental disorders

diagnosed and number of prescribers involved in treatment (MP group only). The most prominent factor associated with the receipt of psychotropic polypharmacy was the involvement of specialist in the treatment. Patients with a specialist involved in the treatment had 5.3 times and 3.6 times higher likelihood of receiving PP in the SP and MP groups respectively (SP: OR=5.324; 95% CI 4.620-6.136 & MP: OR=3.571; 95% CI 3.199-3.985). Other factors positively associated with psychotropic polypharmacy were being a male, Caucasian race, diagnosis of ADHD and bipolar disorder(s). The number of mental/behavioral disorder diagnosed and the number of providers involved in treatment were unique predictors positively associated with polypharmacy in the multiple prescriber group. The Farilie decomposition analysis estimated that the observed need factors explained only approximately 25% of the difference in the receipt of PP between patients seen by PCPs and specialists within both SP and MP groups.

CONCLUSIONS: The most prominent factor associated with PP was involvement of a specialist in the treatment of mental/behavioral disorders. Only a quarter of the difference between PCPs and specialists with respect to prescription of PP was explained by observable need factors, underscoring the drastically different prescribing habits between PCPs and mental health specialists, and the complex implications of pediatric psychotropic polypharmacy.

INTRODUCTION

Clinical guidelines recommend monotherapy as the preferred therapy in the treatment of mental/behavioral disorders. According to the American Academy of Child and Adolescent Psychiatry, data supporting advantageous efficacy for drug combinations is scarce and contemporary clinical evidence supports cautious use of psychotropic drug combinations limiting such use to clinically justifiable circumstances.[1] Simultaneous use of multiple psychotropic medications either from same drug class (within-class psychotropic polypharmacy) or from different drug classes (multiclass psychotropic polypharmacy) has been associated with a number of concerns including adverse events[2,3], drug-drug interactions[4,5], non-adherence[6], higher-healthcare costs[7], morbidity and mortality[8,9]. These concerns are further heightened in children and adolescents as there is limited scientific evidence for understanding the immediate and/or long-term effects of psychotropic polypharmacy on child's growth and development. Also, many psychotropic medications are used "off-label" in this population due to exclusion of this population from clinical trials.[10] Despite these recommendations and concerns the use of psychotropic polypharmacy is quite common in clinical practice.[11-13]

Overall the prevalence of psychotropic polypharmacy ranges from 14% to 73% among pediatric population depending upon the age groups, study designs, data sources and clinical settings.[14-21] Most of the studies that estimated the prevalence of psychotropic polypharmacy have used cross-sectional definitions of polypharmacy measured at a single point of time or within a certain time frame and have been usually based on short-term overlap of medications. However, there are instances where short-term polypharmacy is clearly appropriate or even necessary such as acute amelioration while awaiting the effect of another medication, treating distinct comorbid conditions, boosting the efficacy of primary treatment and treatment of

intervening phases of an illness.[22] The studies that have used long-term (≥60 days) definition of psychotropic polypharmacy have mostly measured within-class polypharmacy only.[23] A study by Chen et al, has used long-term overlap to define both multiclass and within-class psychotropic polypharmacy but they did not study the risk factors associated with the polypharmacy.[14] One study that determined the risk factors associated with multiclass psychotropic polypharmacy used only a 30-day overlap criteria and the population was limited to patients with Autism Spectrum Disorders.[24] Further, it has been established by previous studies that one of the prominent factors associated with polypharmacy is visiting multiple physicians, however in our understanding there has been no study that has attempted to understand whether risk factors associated with psychotropic polypharmacy differ among patients with single prescriber involved in treatment and those with multiple prescribers involved in treatment.

Therefore, the objective of this study was to advance the understanding of the prevalence of and risk factors associated with long-term multiclass psychotropic polypharmacy among children and adolescents with mental/behavioral disorders in a Texas Medicaid population. Additionally, estimates for patients with single prescriber involvement and multiple prescriber involvement were obtained to understand whether risk factors associated with psychotropic polypharmacy differ among these groups.

METHODS

Study Design and Data Source:

This is a retrospective cross-sectional study conducted using the administrative claims data from Texas Children's Health Plan (TCHP) for the period of July 1, 2013 to June 30, 2015. A pre-sampled data of only those children and adolescents who were ever diagnosed with mental/behavioral disorders identified using ICD 9-CM codes (Appendix A) and who had

continuous enrollment throughout the study period was obtained from TCHP. TCHP is the nation's first health maintenance organization (HMO) created just for children. It functions as an administrator for the State Children's Health Insurance Program (CHIP) and STAR/Medicaid managed care programs through a contract with the state Medicaid administrator. TCHP has more than 400,000 members and over 1,100 primary care physicians, 3,200 specialists and 60 hospitals that provide service and patient care to these members. Of the 400,000 members 68% are Hispanics, 16% are Caucasians, 9% are African Americans and the rest are other racial/ethnic groups. The TCHP data provides information on outpatient medical claims, and pharmacy claims. The data also includes information on patient characteristics e.g. patient age, gender, race, and physician characteristics e.g. gender, and specialty. The data is de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) standards. The study was reviewed and approved by the University of Houston Institutional Review Board.

Study Sample:

The study sample consisted of all children and adolescents aged 0 to 18 years who were continuously enrolled in the Texas Children Health Plan, were diagnosed with a mental/behavioral disorder and had at least one pharmacy claim of psychotropic medication during the study period. Psychotropic medications included: drugs for attention-deficit hyperactivity disorder such as stimulants, non-stimulant (atomoxetine), alpha-agonists (guanfacine, clonidine); anti-depressants (selective serotonin norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and tricyclic antidepressants); antipsychotic agents (first and second generation); lithium; anticonvulsant mood-stabilizers (such as divalproex, oxcarbazepine, carbamazepine, lamotrigine), and anxiolytics (such as hydroxyzine and benzodiazepines).

The identified individuals were then categorized into two groups based on the number of prescribers involved in the treatment as: a) single prescriber involved in treatment and b) multiple prescribers involved in treatment.

Measures:

Within each of these study groups the primary outcome of interest was whether an individual had at least one episode of multiclass psychotropic polypharmacy measured as a binary variable (1: Yes, 0: No). Multiclass psychotropic polypharmacy episode was defined as the receipt of 2 or more psychotropic medications from different drug classes concurrently for ≥ 60 days, with no gaps in polypharmacy treatment. The 60-day overlap criterion was used, as it is the most commonly used cutoff used to define polypharmacy, it avoids misclassifying instances of cross-titration as polypharmacy.[23, 24] Patients who received psychotropic medications but did not have a polypharmacy episode at any time during the study period were classified as non-polypharmacy cases. Episodes of treatment were identified using the prescription fill date and the days' supply information available from the pharmacy claims. Before measuring the episodes, overlapping days' supply for the same medication were carried forward assuming that the patient finished the current prescription before starting on the refill prescription. Gaps in fills of the same medication of ≤ 15 days were allowed and adjusted in the calculation of the overlap. Further, the overlap was defined by drug class and not specific medications within class, so it was not necessary for a single medication within a class to overlap by ≥ 60 days with a particular medication in another class. Only unique combinations of drug classes of at least 60 days were considered.

Among patients receiving multiclass psychotropic polypharmacy the secondary outcomes of interest were the duration of polypharmacy episode and the number of polypharmacy episodes

during the study period. Duration of polypharmacy episode was calculated as the number of days from the first date that ≥2 psychotropic medications from different drug classes were received concurrently to the last date that such concurrent medications were received with no gaps in polypharmacy treatment. Number of polypharmacy episodes was calculated as patients could have more than one multiclass psychotropic polypharmacy episode during the study period if they initiated, discontinued and reinitiated on polypharmacy.

Statistical Analysis:

Descriptive statistics, including frequencies, mean (± SD) and median, were used to characterize patient characteristics, number and duration of polypharmacy episodes. Within each of the study groups the differences between non-polypharmacy patients and those experiencing polypharmacy were analyzed using t-tests and Chi-square tests. A-priori significance level of $p<0.05$ was chosen for all comparisons.

Logistic regression was used to determine associations between polypharmacy and independent variables of interest. The independent variables considered include patient age, sex, race; number of mental/behavioral disorders diagnosed; type of mental/behavioral disorder diagnosed; number of prescribers involved in treatment and whether a specialist was involved in treatment. Two separate multivariable models were conducted 1) single-prescriber involved in the treatment and 2) multiple-prescriber involved in treatment.

Post-hoc analysis:

The Farilie decomposition method (extension of Blinder-Oaxaca [BO] decomposition) was used to test the difference in receipt of psychotropic polypharmacy between patients treated by PCPs vs those treated by specialists.[25-28] The aim was to understand the contribution of predisposing (patient age, sex and race) and need factors (number of mental/behavioral disorders

diagnosed; type of mental/behavioral disorder diagnosed; number of prescribers involved in treatment) used in the multivariable model towards explaining the difference between PCP and specialist practice with respect to psychotropic polypharmacy. In the Fairlie's nonlinear method, a 1:1 matching of observations between PCPs and specialists was done to identify the contribution of each of the predisposing and need factors. A random subsample of observations was selected from the majority group (PCPs) and matched to the minority group (specialists), as the number of observations between PCPs and specialists was not equal. The matched sample was then used to estimate the contribution of each factor towards explaining the difference in the receipt of polypharmacy. A 1000 random subsamples of PCPs were used to eliminate the bias due to subsampling. The final decomposition was an average of these subsamples. Separate analysis was conducted for the single prescriber group and the multiple prescriber group.

Sensitivity analysis:

Sensitivity analysis was conducted by using different definitions of multiclass psychotropic polypharmacy, including receipt of 3 or more psychotropic medications from different drug classes concurrently for ≥ 60 days and receipt of 4 or more psychotropic medications from different drug classes concurrently for ≥ 60 days.

Analyses were conducted by using SAS 9.3 software (SAS Institute, Inc, Cary, NC) and STATA12 software (StataCorp, College Station, TX).

RESULTS

A total of 24,147 children and adolescents were diagnosed with a mental/behavioral disorder and had at least one pharmacy claim of psychotropic medication during the study period. The prevalence of multiclass psychotropic polypharmacy was 20.09%. Table M1.1 shows the demographic and clinical characteristics of the children and adolescents on

psychotropic medications in both the single prescriber and multiple prescribers group along with the unadjusted results of differences between the non-polypharmacy and the polypharmacy patients. Majority of the patients in the study sample were male, 62.87% in the single prescriber group and 64.51% in the multiple prescriber group respectively. Substantial differences were observed between the multiple prescriber and single prescriber groups with respect to the diagnosis of attention-deficit hyperactivity disorder (81.69 vs. 68.45, $p<0.001$), bipolar disorder(s) (20.22% vs. 10.73%, $p<0.001$) and depression (17.89% vs 11.96%, $p<0.001$). Also, higher proportion of patients in the multiple prescriber group had a specialist involved in treatment as compared to the single prescriber group (55.42% vs. 40.74%, $p<0.001$).

Single Prescriber involved in treatment:

Non-polypharmacy patients were predominantly Hispanic (46.35%), while patients experiencing psychotropic polypharmacy were predominantly Caucasian (38.10%). The mean age of patients was higher in the polypharmacy group as compared to the non-polypharmacy group (10.15 ± 3.46 vs. 9.66 ± 4.07, $p<0.001$). Higher proportion of patients experiencing psychotropic polypharmacy were diagnosed with multiple mental/behavioral disorders compared to non-polypharmacy cases (60.34% vs. 38%, $p<0.001$). The average number of mental/behavioral disorders diagnosed in the polypharmacy group was higher than the non-polypharmacy group (1.56 ± 0.99 vs. 2.10 ± 1.23, $p<0.001$). The most common diagnosis among both polypharmacy and non-polypharmacy groups was attention-deficit hyperactivity disorder, with polypharmacy group having a substantially higher proportion (84.42% vs. 66.42%, $p<0.001$). Diagnosis of bipolar disorder(s) was almost four times higher among the patients experiencing psychotropic polypharmacy as compared to non-polypharmacy patients (30.34% vs. 8.24%, $p<0.001$). On the other hand, a lower proportion of patients experiencing

psychotropic polypharmacy were diagnosed with learning disorder(s) compared to the non-polypharmacy group (8.71% vs. 14.76%, p<0.001). A substantially higher proportion of patients experiencing psychotropic polypharmacy had a specialist involved in the treatment (79.73% vs. 35.78%, p<0.001) as compared to those patients who were identified as non-polypharmacy.

Multiple Prescribers involved in treatment:

Similar to the single prescriber group, non-polypharmacy patients in the multiple prescriber group were predominantly Hispanic (40.02%), while patients experiencing psychotropic polypharmacy were predominantly Caucasian (45.70%). Patients in the polypharmacy group had a higher mean age as compared to the non-polypharmacy cases (10.08 ± 3.51 vs. 9.80 ± 3.63, p<0.001). Higher proportion of patients experiencing psychotropic polypharmacy were diagnosed with multiple mental/behavioral disorders compared to non-polypharmacy cases (73.27% vs. 47.12%, p<0.001). The average number of mental/behavioral disorders diagnosed in the polypharmacy group was higher than the non-polypharmacy group (1.82 ± 1.15 vs. 2.72 ± 1.60, p<0.001). Patients receiving psychotropic polypharmacy had a relatively higher diagnosis of attention-deficit hyperactivity disorder as compared to non-polypharmacy patients (84.12% vs. 80.62%, p<0.001). About four-times as many patients in the polypharmacy group were diagnosed with bipolar disorder(s) as compared to non-polypharmacy patients (40.17% vs. 11.49%, p<0.001). Higher proportion of patients who experienced psychotropic polypharmacy were diagnosed with depression (26.94% vs. 13.92%, p<0.001), anxiety disorder(s) (22.69% vs. 12.82%, p<0.001) and schizophrenia (11.21% vs. 3.48%, p<0.001) as compared to the non-polypharmacy patients. About twice as many patients experiencing psychotropic polypharmacy had a specialist involved in the treatment (80.12% vs. 44.61%, p<0.001) as compared to those patients who were identified as non-polypharmacy.

About 18% of patients identified as receiving polypharmacy had more than 5 prescribers involved in the treatment, this number was much lower in the non-polypharmacy group (6.15%).

Table M1.2 shows the average number of polypharmacy episodes per patient and the duration of polypharmacy episodes among patients receiving psychotropic polypharmacy. The duration of polypharmacy episodes was longer among patients with multiple prescribers involved in treatment.

Multivariable Logistic Regression:

Table M1.3 summarizes the results of the multivariable regression model. The most prominent factor associated with the receipt of psychotropic polypharmacy was the involvement of specialist in the treatment. Other factors positively associated with psychotropic polypharmacy were being a male, Caucasian race, diagnosis of ADHD and bipolar disorder(s) and involvement of multiple providers in treatment. The number of mental/behavioral disorder diagnosed was not a significant predictor in the single prescriber group but with was positively associated with polypharmacy in the multiple prescriber group.

Single Prescriber involved in treatment:

Patients with a specialist involved in the treatment had 5.3 times higher likelihood of receiving polypharmacy (OR=5.324; 95% CI 4.620-6.136). Males had a 14% higher likelihood of experiencing polypharmacy compared to females (OR=1.140; 95% CI 1.001-1.299). As compared to African Americans, Caucasians were 77% more likely to experience polypharmacy (OR=1.773; 95% CI 1.524-2.063) while Hispanics were 34% less likely to experience polypharmacy (OR=0.657; 95% CI 0.563-0.767). Patients diagnosed with ADHD and bipolar disorder(s) had 3.3 times (OR=3.328; 95% CI 2.595-4.269) and 3.2 times (OR=3.261; 95% CI 2.567-4.142) higher likelihood of experiencing polypharmacy respectively, while patients

diagnosed with adjustment disorder(s) were 40% less likely to experience psychotropic polypharmacy (OR=0.602; 95% CI 0.454-0.798).

Multiple Prescribers involved in treatment:

The likelihood of receiving psychotropic polypharmacy was 3.6 times higher when a specialist was involved in treatment (OR=3.571; 95% CI 3.199-3.985). Males were 20% more likely to experience polypharmacy than females (OR=1.199; 95% CI 1.081-1.330). As compared to African Americans, Caucasians were 89% more likely to experience polypharmacy (OR=1.892; 95% CI 1.672-2.141) while Hispanics were 14% less likely to experience polypharmacy (OR=0.859; 95% CI 0.756-0.977). Each unit increase in the number of mental disorders diagnosed led to a 25% higher probability of experiencing polypharmacy (OR=1.252; 95% CI 1.101-1.425). Diagnosis of ADHD and bipolar disorder(s) was highly associated with psychotropic polypharmacy with 1.8 times (OR=1.761; 95% CI 1.456-2.130) and 2.5 times (OR=2.509; 95% CI 2.091-3.010) higher likelihood among those diagnosed with the respective disorders. On the other hand patients diagnosed with adjustment disorder(s) were 28% less likely to experience psychotropic polypharmacy (OR=0.715; 95% CI 0.588-0.869). Unit increase in the number of prescribers involved in treatment was associated with 40% higher likelihood of receiving polypharmacy (OR=1.409; 95% CI 1.357-1.463).

Post-hoc analysis:

Tables M1.4 and M1.5 report the results for the post-hoc analysis for the difference in polypharmacy use among patients treated by PCPs vs those treated by specialists for both single prescriber and multiple prescriber involvement groups.

Single Prescriber involved in treatment:

Predicted probability of receiving psychotropic polypharmacy was 0.0412 for patients that were prescribed medication by a PCP and 0.2205 for patients that were prescribed medication by specialists. The difference between the two groups was 0.1793 or 17.93 percentage points. The decomposition estimated a coefficient of 0.0477 for the difference between patients visiting PCPs vs the specialists. This means that the observed characteristics explained 26.6% ([0.0477/0.1793]*100) of the difference between the two groups. Predisposing (Race) and need characteristics (diagnosis of bipolar, anxiety and depressive disorders) were the significant factors in the decomposition model. However, only some of the need characteristics viz. diagnosis of bipolar disorders (22.5%), anxiety (1.8%) and depression (3.1%) explained the difference in receipt of polypharmacy between the two groups, while the predisposing factor race had a negative coefficient.

Multiple Prescribers involved in treatment:

Predicted probability of receiving polypharmacy was 0.2713 for patients that were prescribed medication exclusively by PCPs and 0.4195 for patients that involved a specialist in prescription of medications. The difference between the two groups was 0.1482 or 14.82 percentage points. The decomposition estimated a coefficient of 0.0359 for the difference between patients visiting PCPs only vs those with specialists involved in the treatment. This means that the observed characteristics explained 24.2% ([0.0359/0.1482]*100) of the difference between the two groups. Predisposing (patient-age, gender and race) and need characteristics (type of mental disorders diagnosed, number of mental disorders diagnosed and number of providers involved in treatment) were the significant factors in the decomposition model. However, only some of the need characteristics viz. diagnosis of bipolar disorders (42.6%) and depression (7.5%), and total number of mental disorders diagnosed (16.5%) substantially

explained the difference in receipt of polypharmacy between the two groups, while all the predisposing factors and some of the need characteristics had negative coefficients. Other minor factors explaining the difference in receipt of polypharmacy between the two groups were diagnosis of anxiety, learning disorders, ODD and schizophrenia.

Sensitivity analysis:

Risk factors associated with receipt of psychotropic polypharmacy defined using stricter definitions (3 or more psychotropic medications, and 4 or more psychotropic medications) were consistent with the observations of the main analysis. Involvement of specialist was still the single most prominent factor associated with psychotropic polypharmacy. Caucasian race, ADHD and bipolar diagnosis, and number of prescribers involved in the treatment were the positively associated risk factors while Hispanic race and diagnosis of learning and adjustment disorder were negatively associated risk factors for receipt of psychotropic polypharmacy.

DISCUSSION

Prevalence of long-term psychotropic polypharmacy among the sample of a Texas Medicaid population diagnosed with mental/behavioral disorders was about 20%. This finding was consistent with the prevalence reported by Chen et al., in a study conducted among patients of similar age group, comparable study settings and using the same definition of long-term psychotropic polypharmacy.[14] The pattern of psychotropic polypharmacy use suggests that multiple episodes of psychotropic polypharmacy occurred during the study period and continued for longer duration of about 200-230 days which was much higher than expected. Some patients even had episodes of polypharmacy that lasted throughout the two-year study period.

As expected and consistent with the literature[24], receipt of psychotropic polypharmacy was strongly associated with patients' race[29], diagnosis and clinical complexity among both

single prescriber and multiple prescriber treatment groups. Our study identified that the involvement of a specialist (psychiatrist) in patient care was the most prominent factor associated with the receipt of psychotropic polypharmacy even after controlling for the patient demographics, diagnosis and observable measures for clinical complexity. Similar finding was only reported in one published study conducted among children and adolescents with Autism Spectrum Disorders. [23] In addition, we also observed that the likelihood of receiving psychotropic polypharmacy was even higher when specialist was the only prescriber involved in the treatment (single prescriber group), and when polypharmacy was defined as concurrent use of more than three or more than four psychotropic medications.

There are many potential reasons that could explain the differences in the practice of psychotropic polypharmacy between PCPs and specialists. It is known that specialists are more comfortable prescribing psychotropic medications as compared to primary care physicians[30], as they have advanced training in the care and treatment of psychiatric disorders. As compared to PCPs, psychiatrists often emphasize more on symptom reduction rather than the disorder itself leading to prescription of more medications.[31-33] Other than these factors, there is a general belief that the practice difference is mainly because psychiatrists see more severe and clinically complex patients than PCPs.

To advance the understanding of the contribution of predisposing and need factors in explaining the difference in the practice of psychotropic polypharmacy between PCPs and psychiatrists, we conducted a post-hoc analysis using the Fairlie decomposition method (extension of Blinder-Oaxaca [BO] decomposition). The post-hoc analyses showed that only about 25% of the difference in the prescription of psychotropic polypharmacy among PCPs and specialists (in both single and multiple provider groups) was explained by the need factors,

especially the diagnosis of bipolar disorders, depression and anxiety disorders. The number of mental disorders diagnosed was also a significant contributor to the difference in receipt of polypharmacy for the group with multiple prescribers involved in treatment. Predisposing factors like patient age, gender and race had negative coefficients and failed to explain the different prescribing behaviors between these provider specialties. The finding implies that various accesses to mental health specialist may be an important enabling factor that determines the use of long term psychotropic polypharmacy.

Long-term pediatric psychotropic polypharmacy is a concept that often bears negative implication, however, it is needed and well justified in certain occasions. In patients with bipolar disorders evidence-based studies have shown that polypharmacy is more effective than monotherapy.[34] The use of atypical antipsychotic and a mood stabilizer for treatment of acute mania in bipolar patients has been approved by the FDA through two double-blind trials.[35] The treatment guidelines for children and adolescents with bipolar disorders recommends the use of augmented therapy when monotherapy does not work.[36] In adult patients with treatment-resistant depression the use of atypical antipsychotic and antidepressant has been approved by the FDA through a double-blind clinical trial.[37] However, this combination might be used off-label by physicians in treatment of children and adolescents. In such cases, the benefits of these combinations should be weighed against the risk of adverse events such as weight gain and hyperlipidemia.

In our study we found that polypharmacy is a practice predominantly driven by the best-trained group of providers: mental health specialists, and the observable need factors could only explain a quarter of the differences in practice. Even though some measures of clinical complexity, such as functional impairment, are not available in our data, the finding still

reiterates that psychotropic polypharmacy is a practice for which the significance and implication varies based on individual cases. It may not be appropriate to make a general judgment whether it is good or bad for patients. To ensure patient safety, the emphasis should be placed on promoting sufficient monitoring of potential drug-drug interaction, adverse drug events, and improving care coordination when multiple providers are involved in a care team.

There were some limitations to the study; the main limitation was that due to cross-sectional nature of analysis only associations could be made between risk factors and polypharmacy. Secondly, like any other administrative claims based study, the findings of this study were based on the data of dispensed medications and do not confirm actual consumption by the patients. However, theoretically repeated fills of the medication are indicative of actual use. Furthermore, the information on patient's medical history, patient preferences, disease severity and reason for medication prescription cannot be obtained from claims data, thus prohibiting the determination of their association with psychotropic polypharmacy.

CONCLUSIONS

The study highlights the extent of psychotropic polypharmacy use in the treatment of children and adolescents with mental/behavioral disorders. The most prominent factor associated with PP was involvement of a specialist in the treatment of mental/behavioral disorders. Only a quarter of the difference between PCPs and specialists with respect to prescription of PP was explained by observable need factors, underscoring the drastically different prescribing habits between PCPs and mental health specialists, and the complex implications of pediatric psychotropic polypharmacy.

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Table M1. 1 Demographic and clinical characteristics

Characteristic	Single Prescriber involved in treatment (N=13,045; 54.02%)		Multiple Prescribers involved in treatment (N=11,102; 45.98%)	
	Non-polypharmacy (N=11,575; 88.73%)	Psychotropic polypharmacy (N=1,470; 11.27%)	Non-polypharmacy (N=7,721; 69.55%)	Psychotropic polypharmacy (N=3,381; 30.45%)
Sex				
Male	7220 (62.38)	981 (66.73)	4976 (64.46)	2187 (64.69)
Race				
African American	2733 (23.61)	411 (27.96)	1836 (23.78)	709 (20.97)
Alaskan	27 (0.23)	5 (0.34)	29 (0.38)	10 (0.30)
Asian	175 (1.51)	7 (0.48)	101 (1.31)	31 (0.92)
Caucasian	2908 (25.13)	560 (38.10)	2445 (31.67)	1545 (45.70)
Hispanic	5364 (46.35)	452 (30.75)	3090 (40.02)	1013 (29.96)
Not reported	367 (3.17)	35 (2.38)	220 (2.85)	73 (2.16)
Age group				
0-3	691 (5.97)	8 (0.54)	196 (2.54)	36 (1.06)
4-8	4197 (36.26)	548 (37.28)	2915 (37.75)	1216 (35.97)
9-12	3455 (29.85)	500 (34.01)	2624 (33.99)	1165 (34.46)
13-18	3232 (27.92)	414 (28.16)	1986 (25.72)	964 (28.51)
Mean (± SD)	9.66 (4.07)	10.15 (3.46)	9.80 (3.63)	10.08 (3.51)
Number of mental/behavioral disorders diagnosed				
0	562 (4.86)	12 (0.82)	132 (1.71)	16 (0.47)
1	6615 (57.15)	571 (38.84)	3951 (51.17)	888 (26.26)
2-4	4214 (36.41)	814 (55.37)	3371 (43.66)	1997 (59.07)
≥5	184 (1.59)	73 (4.97)	267 (3.46)	480 (14.20)
Mean (± SD)	1.56 (0.99)	2.10 (1.23)	1.82 (1.15)	2.72 (1.60)
Type of mental/behavioral disorder diagnosed				
ADHD	7688 (66.42)	1241 (84.42)	6225 (80.62)	2844 (84.12)
Bipolar Disorder(s)	954 (8.24)	446 (30.34)	887 (11.49)	1358 (40.17)
Depression	1315 (11.36)	245 (16.67)	1075 (13.92)	911 (26.94)
Anxiety	1308 (11.30)	217 (14.76)	990 (12.82)	767 (22.69)
Learning Disorder(s)	1708 (14.76)	128 (8.71)	954 (12.36)	329 (9.73)
Adjustment Disorder(s)	1112 (9.61)	134 (9.12)	822 (10.65)	516 (15.26)
Conduct Disorder	1144 (9.88)	202 (13.74)	881 (11.41)	4.70 (15.44)

Oppositional Defiant Disorder	832 (7.19)	220 (14.97)	828 (10.72)	753 (22.27)
Schizophrenia	297 (2.57)	63 (4.29)	269 (3.48)	379 (11.21)
Number of prescribers involved in treatment				
2-4	NA	NA	7246 (93.85)	2780 (82.22)
≥5	NA	NA	475 (6.15)	601 (17.78)
Mean (± SD)	NA	NA	2.66 (1.05)	3.34 (1.55)
Hospitalization/ ER-visit				
Yes	1103 (9.53)	202 (13.74)	1205 (15.61)	1045 (30.91)
Specialist visited				
Yes	4142 (35.78)	1172 (79.73)	3444 (44.61)	2709 (80.12)

Table M1. 2 Summary of psychotropic polypharmacy use

Parameter	**Psychotropic polypharmacy** (N=4,851; 20.09%)					
	Single Prescriber (N=1470; 30.30%)			**Multiple Prescribers** (N=3381; 69.70%)		
	Mean ± S.D.	Median	Range	Mean ± S.D.	Median	Range
Polypharmacy episodes per polypharmacy user	1.43 ± 0.68	1	1-5	1.48 ± 0.72	1	1-5
Duration of polypharmacy episodes (number of days)	265.06 ± 192.80	201.5	60-730	283.63 ± 192.61	229.0	60-730

Table M1. 3 Multivariable Logistic Regression

Characteristic	Single Prescriber involved in treatment				Multiple Prescribers involved in treatment			
	OR	95% CI		P	OR	95% CI		P
		LL	UL			LL	UL	
Age								
Age	1.002	0.984	1.020	0.827	0.974	0.959	0.989	<0.001
Sex (Ref: Female)								
Male	1.140	1.001	1.299	0.049	1.199	1.081	1.330	<0.001
Race (Ref: African American)								
Alaskan	2.064	0.677	6.288	0.203	1.154	0.498	2.671	0.739
Asian	0.345	0.156	0.764	0.009	1.169	0.734	1.861	0.511
Caucasian	1.773	1.524	2.063	<0.001	1.892	1.672	2.141	<0.001
Hispanic	0.657	0.563	0.767	<0.001	0.859	0.756	0.977	0.020
Not reported	1.238	0.834	1.839	0.290	1.194	0.872	1.633	0.269
Number of mental/behavioral disorders diagnosed								
No. of MHD	1.046	0.87	1.257	0.633	1.252	1.101	1.425	<0.001
Type of mental/behavioral disorder diagnosed (Ref: No)								
ADHD	3.328	2.595	4.269	<0.001	1.761	1.456	2.130	<0.001
Bipolar Disorder(s)	3.261	2.567	4.142	<0.001	2.509	2.091	3.010	<0.001
Depression	1.437	1.101	1.876	0.008	1.158	0.949	1.412	0.149
Anxiety	1.413	1.085	1.84	0.010	1.148	0.948	1.390	0.157
Learning Disorder(s)	0.749	0.561	1.001	0.050	0.658	0.532	0.814	<0.001
Adjustment Disorder(s)	0.602	0.454	0.798	<0.001	0.715	0.588	0.869	<0.001
Conduct Disorder	1.153	0.882	1.505	0.298	0.705	0.578	0.860	<0.001
Oppositional Defiant Disorder	1.141	0.879	1.481	0.323	1.007	0.836	1.214	0.941
Schizophrenia	1.016	0.701	1.474	0.932	1.278	1.004	1.628	0.046
Hospitalization/ER visit (Ref: No)								
Yes	1.139	0.938	1.382	0.189	1.016	0.891	1.158	0.815
Number of prescribers involved in treatment								
No. of Prescribers	NA	NA	NA	NA	1.409	1.357	1.463	<0.001
Specialist Visited (Ref: No)								
Yes	5.324	4.62	6.136	<0.001	3.571	3.199	3.985	<0.001

Table M1. 4 Nonlinear decomposition of psychotropic polypharmacy use between patients treated by PCPs and specialists

Probability of receiving psychotropic polypharmacy for patients treated by PCPs				0.0412
Probability of receiving psychotropic polypharmacy for patients treated by specialists				0.2205
Difference in psychotropic polypharmacy use				0.1793
Independent variables	Decomposition	Standard error	P value	% Contribution
Predisposing Characteristics				
Age	0.0001	0.0009	0.882	0.06
Male	-0.0002	0.0003	0.436	0.11
Race	-0.0082	0.0013	0.000	-4.57
Need Characteristics				
Number of mental/behavioral disorders diagnosed	0.0048	0.0090	0.598	2.68
ADHD	0.0011	0.0015	0.477	0.61
Bipolar Disorder(s)	0.0403	0.0044	0.000	22.48
Depression	0.0055	0.0022	0.013	3.07
Anxiety	0.0033	0.0015	0.028	1.84
Learning Disorder(s)	0.0003	0.0004	0.440	0.17
Adjustment Disorder(s)	-0.0030	0.0010	0.004	-1.67
Conduct Disorder	0.0009	0.0009	0.327	0.50
Oppositional Defiant Disorder	0.0019	0.0021	0.375	1.06
Schizophrenia	-0.0001	0.0008	0.927	0.06
Hospitalization/ER visit	0.0011	0.0010	0.273	0.61
Total explained by measurable characteristics	0.0477			26.60

Table M1. 5 Nonlinear decomposition of psychotropic polypharmacy use between patients treated by PCPs and specialists

Probability of receiving psychotropic polypharmacy for patients treated by PCPs				0.2713
Probability of receiving psychotropic polypharmacy for patients treated by specialists				0.4195
Difference in psychotropic polypharmacy use				0.1482
Independent variables	Decomposition	Standard error	P value	% Contribution
Predisposing Characteristics				
Age	-0.0052	0.0017	0.003	-3.51
Male	-0.0032	0.0008	0.000	-2.16
Race	-0.0184	0.0014	0.000	-12.42
Number of mental/behavioral disorders diagnosed	0.0244	0.0095	0.010	16.46
ADHD	-0.0170	0.0025	0.000	-11.47
Bipolar Disorder(s)	0.0631	0.0048	0.000	42.58
Depression	0.0111	0.0035	0.002	7.49
Anxiety	0.0060	0.0020	0.002	4.05
Learning Disorder(s)	0.0008	0.0004	0.025	0.54
Adjustment Disorder(s)	-0.0026	0.0011	0.014	-1.46
Conduct Disorder	-0.0016	0.0006	0.011	-1.08
Oppositional Defiant Disorder	0.0045	0.0017	0.006	3.04
Schizophrenia	0.0048	0.0016	0.002	3.24
Hospitalization/ER visit	0.0011	0.0021	0.600	0.74
Number of prescribers involved	-0.0321	0.0016	0.000	-21.6
Total explained by measurable characteristics	0.0359			24.22

MANUSCRIPT 2

Association between Physician Care Coordination and the Use of Psychotropic Polypharmacy in the Management of Pediatric Mental Disorders.

Abstract

BACKGROUND: Psychotropic polypharmacy has been a main safety concern in the management of pediatric mental disorders. Although seeing multiple providers has been identified as an important predictor for the receipt of polypharmacy, no study has yet assessed the impact of care coordination between providers.

OBJECTIVE: To examine the association between the intensity of care coordination within a patient's care team and the likelihood of the patient receiving psychotropic polypharmacy.

METHODS: A retrospective cross-sectional study was conducted using the 2013-2015 administrative claims data from a Medicaid Managed Care Organization (Texas Children's Health Plan). The study included individuals: a) ≤18 years of age, b) diagnosed with a mental disorder, and c) received psychotropic prescriptions from multiple prescribers. Psychotropic polypharmacy (PP) was defined as the receipt of ≥ 2 psychotropic medications from different drug classes concurrently for 60 days or more. Care coordination was measured using Care-density (CD), a surrogate included in the AHRQ Care Coordination Measures Atlas, calculated as the ratio of the sum of patients shared by physician pairs within a patient's care team to the total number of physician pairs. Guided by Andersen behavioral model, multivariate logistic regression analyses were conducted to assess the association between CD and patients' likelihood of receiving PP after controlling for predisposing and need factors.

RESULTS: A total of 24,147 children and adolescents who met the inclusion criteria were identified. Nearly half (n=11,102; 45.98%) of these individuals received PP prescribed by multiple providers. Logistic regression analysis showed a significant association between care density and the use of psychotropic polypharmacy. However, the direction of this relationship varied depending on the composition of the patient's care team. Among patients with only PCPs

involved in their care team, patients in the higher CD group were 84% less likely to receive PP (OR=0.156; 95% CI 0.056-0.432) than those in low CD group. In contrast, among patients who had both PCPs and specialists involved in their care team, those in the higher CD group were 2.4 times more likely to experience PP (OR=2.441; 95% CI 1.899-3.137). CD was not significantly associated with the receipt of PP in specialists only group.

CONCLUSIONS: To the opposite from what has been perceived, higher care density between primary care providers and specialists resulted into increased use of psychotropic polypharmacy in children and adolescents.

INTRODUCTION

Despite the recommendations of clinical guidelines[1] for the use of monotherapy in the treatment of children and adolescents with mental/behavioral disorders, the use of polypharmacy (concurrent use of medications) is quite common in psychiatric care with the overall prevalence ranging from 14% to as high as 73%.[2-9] Psychotropic polypharmacy has heightened public health concern, because there is limited scientific evidence for understanding the immediate and/or long-term effects of its use on child's growth and development. Additionally, psychotropic polypharmacy has been associated with a number of negative consequences including adverse events[10,11], drug-drug interactions[12,13], non-adherence[14], higher-healthcare costs[15], morbidity and mortality.[16,17]

Due to the growing concerns, the State Medicaid Agencies in about 42 states in the United States have employed programs to monitor the prescribing of psychotropic medications in children.[18] The Psychotropic Medication Utilization Review (PMUR) is one such set of parameters implemented by the State of Texas which monitors the psychotropic medication utilization in foster care children and has led to reduction in the inappropriate use of psychotropic medications in the Texas foster care population.[19] However, the major limitation of these parameters is that it views inappropriate use of psychotropic medications as the outcome individual prescriber's knowledge and attitude. The whole emphasis of these parameters is on the non-concordant behavior of a single individual physician providing care for the patient. It fails to acknowledge that some out-of-parameter uses, especially psychotropic polypharmacy, could arise from poor communication among providers rather than due to individual prescriber's non-concordant behavior. Previous studies have shown that involvement of multiple physicians in the provision of care is significantly associated with the receipt of polypharmacy.[20, 21] Fragmented

care and lack of coordination among the physicians in the patient's care team can lead to continuation of psychotropic polypharmacy in cases where it is not medically essential.[22]

Care coordination involves deliberate organization of patient care activities such as accurate transfer of information, adequate communication, and appropriate follow-up care.[23, 24] Efficient channels of communication and collaboration among physicians are recognized catalysts to improved patient care.[25] It allows input from multiple providers caring for the same patient, which produces decisions based on complete information, which in turn leads to better patient outcomes. Thus, in this study we want to examine whether better care coordination reduces the chances of receiving psychotropic polypharmacy.

Recently, the concepts and techniques of social network analysis have been used to characterize the professional relationships among providers that result from day-to-day interactions, patient referrals and shared patients. Researchers have used the number of shared patients as an indicator of the strength of provider collaborative relationship. Pollack et al developed a measure called care-density, which determines the extent of patient sharing among physicians.[26] It is hypothesized that providers who share greater number of patients have stronger collaborative relationships and will be able to provide better-coordinated care. A study by Barnett et al has validated that physicians who shared 8 or more patients had 80% probability of having an information-sharing relationship. [27] Several studies have demonstrated direct association between care-density and healthcare outcomes such as quality of care, cost of care and hospital outcomes. A study by Pollack et al, conducted using administrative databases from 3 large commercial insurance plans showed that higher care-density was associated with lower odds of adverse events and 30-day readmissions in some of these settings.[28] Another study by Pollack et al, showed that, among patients with congestive heart failure and diabetes, higher

care-density was associated with lower inpatient costs and reduced rates of hospitalization in the CHF cohort and lower outpatient costs but higher pharmacy costs in the diabetes cohort.[26] A study by Ong et al examined the effect of care-density on multiple provider prescribing of benzodiazepines, it was found that provider pairs who shared greater number of patients were less likely to co-prescribe overlapping benzodiazepines.[29] However, to our knowledge there has been no study that has looked at the relationship between care-density and psychotropic polypharmacy.

Therefore, the objective of this study was to examine the relationship between care-density and receipt of psychotropic polypharmacy among children and adolescents with mental/behavioral disorders. Further, we examined if this relationship varies depending on the specialty of physicians involved in the care team.

METHODS

Study Design and Data Source:

A retrospective cross-sectional study was conducted using the administrative claims data from Texas Children's Health Plan (TCHP) for the period of July 1, 2013 to June 30, 2015. Data was obtained for children and adolescents who were ever diagnosed with mental/behavioral disorders identified using ICD 9-CM codes (Appendix A) and who had continuous enrollment throughout the study period. TCHP is the nation's first health maintenance organization (HMO) created just for children. It is an administrator for the State Children's Health Insurance Program (CHIP) and STAR/Medicaid managed care programs through a contract with the state Medicaid administrator. TCHP has more than 400,000 members and over 1,100 primary care physicians, 3,200 specialists and 60 hospitals that provide service and patient care to these members. TCHP data contains information on outpatient medical claims, and pharmacy claims. It also provides

information on the physician that was involved in the care/treatment during each patient visit (claim) such as the physician ID, gender, and specialty. Additionally, the data includes information on patient characteristics e.g. patient age, gender, and race. The data is de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) standards.

Study Sample:

The study included individuals who: a) were 0 to 18 years of age (children and adolescents), b) were diagnosed with a mental/behavioral disorder, c) had at least one pharmacy claim of psychotropic medication, and d) received prescription for psychotropic medication from multiple (at least two) prescribers during the study period. Further, these individuals were required to be continuously enrolled in the Texas Children Health Plan. Individuals who received prescription of psychotropic medication from a single prescriber throughout the study period were excluded from the study. The psychotropic medications considered in the study included: medications for attention-deficit hyperactivity disorder such as stimulants, non-stimulant (atomoxetine), alpha-agonists (guanfacine, clonidine), anti-depressant medications (selective serotonin norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and tricyclic antidepressants); antipsychotic agents (first and second generation); lithium; anticonvulsant mood-stabilizers (such as divalproex, oxcarbazepine, carbamazepine, lamotrigine), and anxiolytics (such as hydroxyzine and benzodiazepines).

Outcome Measure:

The outcome of interest was whether an individual had at least one episode of multiclass psychotropic polypharmacy during the study period, measured as a binary variable (1: Yes, 0: No). An episode of multiclass psychotropic polypharmacy was defined as the receipt of ≥ 2 psychotropic medications from different drug classes concurrently for 60 days or more, with no

gaps in polypharmacy treatment. The 60-day overlap criterion is the most commonly implemented cutoff used to define polypharmacy, it avoids misclassifying instances of cross-titration as polypharmacy. Patients who received psychotropic medications but did not have a polypharmacy episode at any time during the study period were classified as non-polypharmacy cases. Episodes of treatment were identified using the prescription fill date and the days' supply information available from the pharmacy claims. Before measuring the episodes, overlapping days' supply for the same medication were carried forward assuming that the patient finished the current prescription before starting on the refill prescription. Gaps in fills of the same medication of ≤ 15 days were allowed and adjusted in the calculation of the overlap. Further, the overlap was defined by drug class and not specific medications within class, so it was not necessary for a single medication within a class to overlap by ≥ 60 days with a particular medication in another class. Only unique combinations of drug classes of at least 60 days were considered.

Exposure Measures:

The Andersen behavioral model was used to guide the selection of the potential predictors that could help explain the variation in the receipt of psychotropic polypharmacy among children with mental disorders. The components of the model including predisposing, enabling and need factors were defined based on literature and the relevance to the study's objective. Predisposing factors included patient's age, sex and race. Patient's care team density was considered as the enabling factor. Need factors included number of mental/behavioral disorders diagnosed, type of mental/behavioral disorder diagnosed, and number of prescribers involved in treatment.

Care-density was the primary independent variable of the study. To measure the care density, a physician patient-sharing network was first constructed using the pharmacy claims

data. A pair of physician was considered to have shared a patient if they both prescribed medications to a given patient anytime during the study period. A tie formed through such patient sharing was called a network tie. A set of all such possible ties between all the physicians in the data formed the physician patient-sharing network. Number of patients shared between physicians was used to characterize the collaborative relationships between the physicians. The extent of patient-sharing among the physicians was estimated using the "Care-Density" measure developed by Pollack et al. Care-Density is a patient-level measure, calculated as the ratio of the sum of patients shared by physician pairs within a patient's care team to the total number of physician pairs within the patient's care team.[26] Figure M2.1 illustrates with example the calculation of Care-Density. Care-density corresponds to the care team's cohesiveness, which is theoretically a representation of effective collaboration and communication between the patient's care team. A greater Care-density value indicates stronger care team cohesiveness. Care-density was operationalized as a binary variable (0: CD <median and 1: CD ≥ median).

Considering that patients with differing disease complexity might be treated by care teams consisting of various type of providers (e.g. PCPs only, or combination of PCPs and specialists, or even by multiple specialists), and that the need and the purpose of care coordination, and the actual information exchanged might differ between PCP-PCP, PCP-specialist or specialist-specialist, stratification by physician specialty was necessary. To understand the variant implications of Care-Density on psychotropic polypharmacy in different types of patient's care team, four patient groups were created based on the type of physicians involved in the care team: a) Primary Care Physicians (PCPs) only (e.g. general medicine, family medicine, and internal medicine), b) Specialists only (e.g. psychiatry, addiction medicine, psychosomatic medicine), c) PCPs and Specialists, and d) Others.

Statistical Analysis:

Descriptive statistics, including frequencies, mean (± SD) and median were used to characterize patients' demographics, clinical characteristics, and Care-Density. Separate Logistic regression models were fitted for patients with different types of care team to determine associations between Care-Density and the receipt of multiclass psychotropic polypharmacy after controlling for predisposing and need factors.

A-priori significance level of $p<0.05$ was chosen for the analyses. All analyses were conducted by using SAS 9.3 software (SAS Institute, Inc, Cary, NC).

The study was reviewed and approved by the University of Houston Institutional Review Board.

RESULTS

A total of 24,147 children and adolescents were diagnosed with a mental/behavioral disorder and had at least one pharmacy claim of psychotropic medication during the study period. Nearly a half (n=11,102; 45.98%) of these psychotropic medication recipients received the prescriptions from multiple prescribers. According to the types of providers involved in prescribing, the 11,012 patients were divided into the following 4 groups: PCPs only (n=3,408; 30.70%), specialists only (n= 1,921; 17.30%), PCP and specialists (n= 2,763; 24.89%); and other physician group (n=3,010; 27.11%). Table M2.1 presents the demographic and clinical characteristics of the patients in each of these groups.

Patient characteristics:

Patients in the 4 groups created based on types of care team varied in terms of age, race, type of mental disorders diagnosed, number of comorbid mental disorders, and the likelihood of having hospitalization/ER visits. Specifically, Caucasians were more likely to see PCPs, while

minorities especially Hispanics were more likely to see specialists. More than 90% of patients with PCP only care team were diagnosed with ADHD, while in teams with specialist involvement, especially specialist only team there were significantly higher proportion of patients with depression, bipolar disorders, and schizophrenia.

Receipt of psychotropic polypharmacy:

The PCP + Specialist group was the group that had the highest utilization rate of psychotropic polypharmacy (42.89%), followed by specialist only group (40.50%), other physician group (33.55%), and with the lowest observed among the PCP only group (12%). The differences in demographic and clinical characteristics between the non-polypharmacy and the polypharmacy recipients by study groups are presented in Table M2.2.

Predisposing factors:

Across all study groups, majority of the patients in both psychotropic polypharmacy and non-polypharmacy group were male. Patients in the non-polypharmacy group were predominantly Hispanic, while patients in the psychotropic polypharmacy group were predominantly Caucasian. The average age of children in all the groups was about 10 years.

Need Characteristics:

A substantially higher proportion of patients experiencing psychotropic polypharmacy were diagnosed with multiple mental/behavioral disorders compared to non-polypharmacy cases. Similarly, higher number of patients identified as receiving psychotropic polypharmacy had more than 5 prescribers involved in the treatment, as compared to the non-polypharmacy group. Higher proportion of patients experiencing polypharmacy were ever hospitalized or visited ER during the study period as compared to the non-polypharmacy cases.

Enabling factors:

Unlike the consistent differences observed on predisposing and need factors between polypharmacy recipient and non-recipients across the study groups, the implication of care density to receipt of psychotropic polypharmacy varies significantly across the study groups involving different types of prescribers.

The median care-density was higher among the non-polypharmacy recipients compared to the polypharmacy recipients among the PCP only and specialist only groups. In contrast, the median care-density was lower in the non-polypharmacy recipients compared to the polypharmacy recipients in the PCP + specialist and the other physician group. Higher care-density corresponds to stronger care team cohesiveness, suggesting that the care teams of the patients were more cohesive and integrated.

Multivariable Logistic Regression:

Table M2.3 presents the results for analysis conducted for each patient groups created on the basis of specialty of physicians involved in the patient care team. Median care density was used as the cutoff between high and low care density in all models.

Enabling Characteristics:

a) PCPs only: Among patients with only PCPs involved in the patient care team, patients in the high care-density group were 28% less likely to receive psychotropic polypharmacy (OR=0.722; 95% CI 0.618-0.963).

b) Specialists only: Care density was not significantly associated with the receipt of psychotropic polypharmacy among patients who received psychotropic prescriptions from multiple specialists.

c) PCPs and Specialists: Among patients who had both PCPs and specialists involved in their care team, those who received care from a provider team with higher care-density were 2 times

more likely to experience psychotropic polypharmacy (OR=2.006; 95% CI 1.680-2.397) than the ones whose care team had lower care-density.

d) Others: In this group of patients, higher care-density was associated with 1.3 times higher probability of experiencing psychotropic polypharmacy (OR=1.295; 95% CI 1.07-1.563).

Predisposing Characteristics:

In all the groups Caucasians had a higher likelihood of receiving psychotropic polypharmacy than African Americans. The direction of the effect estimates for age, and gender were also consistent across the study groups. However, statistically significant differences were only detected among some provider groups. Each year increase of age was associated with about 4% decrease in the probability of receiving psychotropic polypharmacy among the PCP + specialist group (OR=0.966; 95% CI 0.938-0.994). Males had a 46% higher probability of receiving psychotropic polypharmacy than females in the PCP only group (OR=1.464; 95% CI 1.135-1.889).

Need Characteristics:

Increase in the number of prescribers involved in the treatment was associated with higher likelihood of receiving psychotropic polypharmacy among all the groups. Increase in the number of mental disorders diagnosed was associated with higher likelihood of receiving psychotropic polypharmacy in the PCP only and PCP + specialist groups. Diagnosis of learning disorder was associated with decreased probability of receiving psychotropic polypharmacy among the patients in PCP only, PCP + specialist and the other physician groups. Patients diagnosed with ADHD, bipolar disorder and depression had a higher probability of receiving psychotropic polypharmacy in the specialist only and other physician group than those not diagnosed with these disorders.

DISCUSSION

This is the first study to examine the association between physician patient-sharing relationships and prescription of psychotropic polypharmacy, using the concepts of social network analysis. The primary finding of our study is that among the sample of Medicaid population enrolled in the Texas Children's Health Plan, who were diagnosed and treated for mental/behavioral disorder(s), it was found that the enabling factor representing the extent of patient sharing between the patient's care team (i.e. care-density) was strongly associated with the likelihood of receiving psychotropic polypharmacy. However, the relationship between care-density and psychotropic polypharmacy varied depending on the specialty of physicians involved in the care team. It was observed that, among the patients with only primary care physicians involved in the care team, higher care-density was associated with lower likelihood of receiving psychotropic polypharmacy. Similar finding was observed in the patients whose care team composed of physicians other than PCPs and/or specialists. On the other hand, in the group of patients who either only had specialists in the care team or had both PCPs and specialists, higher care-density was associated with higher likelihood of receiving psychotropic polypharmacy.

The various implications of care density in patient groups seen by different care teams could be because the study groups represent patients of differing diagnosis, clinical complexity, and therefore of differing needs for psychotropic polypharmacy. When the care team consists of PCPs only, nearly 90% of patients had a single ADHD diagnosis. The clinical practice guidelines for diagnosis and treatment of ADHD recommends the use of either behavioral therapy, medication or a combination of behavioral therapy and medication for the treatment of uncomplicated ADHD depending on the age of the child.[30] Combination or augmentation therapy is not recommended for management of ADHD unless the patient is diagnosed with

comorbid conditions like bipolar disorders, tics or anxiety disorders in which case short-term polypharmacy might be used.[31] Moreover, seeing multiple PCPs does not suggest increased clinical complexity in our study. It rather implies that the patients either changed his/her primary care provider or receipt of prescriptions from multiple PCPs from a shared practice as TCHP is a HMO that requires the patient to select a primary care provider as the primary contact of most medical concerns. The patient group who were seen by multiple mental health specialists are distinctively different from the group that had only PCPs in their care team. Children and adolescents in this group had much higher prevalence of mood disorders, especially bipolar disorder and depression as compared to patients who have seen PCPs only. Use of psychotropic polypharmacy in treatment of bipolar disorders is quite common in clinical practice. Evidence-based studies have shown that polypharmacy is more effective than monotherapy in some bipolar disorder patients. Combination treatment with atypical antipsychotic and a mood stabilizer for acute mania has been approved by FDA through two double-blind trials.[32] The treatment guidelines for children and adolescents with bipolar disorders recommends the use of augmented therapy when monotherapy does not work.[33] The combination of atypical antipsychotic and antidepressant has been approved by FDA based on a double-blind clinical trial[34] for adult patients with treatment-resistant depression. However, this combination might be used off-label by physicians in treatment of children and adolescents with treatment-resistant depression. Moreover, this group is also the most severe subgroup with respect to clinical complexity. About 32% percent of children and adolescents in this sub-cohort had either been hospitalized or had an ER-visit and about 75% had multiple comorbid psychiatric disorders. Therefore, children and adolescents in this group are in great need of intensive pharmacotherapy including psychotropic polypharmacy. The patients who have received psychotropic prescriptions from both PCPs and

specialists had diagnostic profile and clinical complexity more similar to patients who received care from multiple providers than those received care from PCPs only. These patients often are identified by their PCPs or self-identified as needing specialty care which implies that treatment escalation or adjustment is expected. The last group represents patients who were prescribed psychotropic medications by non-specialist, non-PCP physicians. Some of these patients were also prescribed medications by PCPs and specialists but the majority of the care is provided by non-PCP, non-specialist physicians. These type of physicians usually provide prescriptions for maintenance therapy and are conservative in their approach like PCPs. Care-coordination strategies in these group might be focused more towards adequacy of treatment and maintenance therapy, thus the observed negative relationship with polypharmacy.

Care density is a surrogate measure for care communication and collaboration. It is based on the concept and methods of social network analysis and patient-sharing. Networks built on the basis of patient-sharing relationships have been previously validated by Barnett et al.[27] Care-density as a measure of collaboration and coordination has been used to study healthcare outcomes related to quality of care, cost of care and hospital admissions.[26, 28] Care coordination is defined as "the deliberate organization of patient care activities between two or more participants involved in a patient's care to facilitate the appropriate delivery of health care services"[35] The purpose of collaboration is to better meet the need of patients, provide sufficient treatment, and reduce redundancy and medication errors. Probably due to the various needs of each patient subgroup on psychotropic polypharmacy, the care collaboration therefore had different implications. Specifically, higher care density or better care coordination leads to less use of psychotropic polypharmacy in patients with uncomplicated ADHD (those who see PCPs only), but increased use among the more severe cases with bipolar disorders or multiple comorbid

mental disorders who are seeking for specialty care (those who see both PCP and psychiatrists). For those clinically complex patient group who have seen multiple psychiatrists, polypharmacy might be justified or might even be a norm, thus, probably care-coordination does not play a major role in prescription of polypharmacy.

Our study suggests that the receipt of psychotropic polypharmacy, is not only determined by predisposing and need factors as reported in the previous literature[36, 37], but also strongly associated with enabling factor such as care collaboration within a patient's care team. For patients who have ever seen by a specialist, higher care density is either associated with increased use of psychotropic polypharmacy (PCP+ specialists, other specialists), or had no impact on its utilization (multiple specialists). The findings suggest that, to the opposite from the stigma associated with pediatric psychotropic polypharmacy, the practice is mainly resulting from a patient's clinical complexity and improved collaboration within the patient's care team. Psychotropic polypharmacy might be needed in these patients and the utilization could be well justified. Appropriate follow-up and monitoring of these patients is all the more important to make sure that psychotropic polypharmacy is effective in reducing symptoms and not leading to unwanted side effects. Number of prescribers involved was a strong predictor of psychotropic polypharmacy, thus it can be said that care-density alone is not adequate representation of care coordination, other aspects of coordination should also be explored. Further research is needed to understand the drug-drug interaction, sufficiency of monitoring.

Recently, the "Care Coordination Measures Atlas Update" developed for the Agency for Healthcare Research and Quality (AHRQ) elaborated on Social Network Analysis as an emerging method for the measurement of care coordination.[37] Patient sharing networks developed using the concepts of Social Network Analysis represent a probable mechanism of

care coordination. Early work by Barnett et al[27], Pollack et al[26, 28], Ong et al[29] and others is promising and has shown that care density is independently associated with various aspects of health care such as quality of care, prescribing error rates and costs. Our study adds to this pool of research and advances the understanding of using patient sharing networks to measure care coordination in mental health care.

There were several limitations to this study. First, this was a cross-sectional study thus the longitudinal continuity of care could not be measured. Only associations between patient-sharing and psychotropic polypharmacy were determined. Second, the structural features of the relationships between physicians such as practice size, type of practice and geographical variations could not be adjusted for during the development of patient-sharing networks. Third, care-density was calculated as a claim based measure of coordination on the assumption that physicians who share more patients are more likely to collaborate, however whether care was actually coordinated for a given patient could not be estimated using the current data. Lastly, clinical severity of the patient could not be assessed using the claims data. Third, even though physicians share high number of patients it is possible that these physicians do not necessarily exchange information on particular patient's care plan, rather communicate about their practice in general. Lastly, care-density might be affected by the structure of health care organizations (size of practice, mode of information exchange, and type of practice), which could not be accounted for in this study.

CONCLUSIONS

This study found significant associations between care-density and psychotropic polypharmacy. It was further observed that this relationship varied depending on the composition of the patient's care team. Care-density as a measure of care coordination is still in its developing

stages, however it might be possible to use care-density in combination with other measures of care coordination to completely characterize multiple aspects of coordination. It can act as a supplement to the existing parameters implemented by State Medicaid agencies to identify patients at higher risk of psychotropic polypharmacy and to employ interventions for improving care coordination.

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Table M2. 1 Demographic and clinical characteristics by study groups.

Characteristic	Multiple prescribers involved in treatment (N=11,102; 100%)			
	PCPs only (N=3,408)	Specialists only (N=1,921)	PCP + Specialist (N=2,763)	Others (N=3,010)
PREDISPOSING CHARACTERISTICS				
Sex				
Male	2367 (69.45)	1135 (59.11)	1804 (65.29)	1857 (61.69)
Race				
African American	689 (20.22)	477 (24.83)	645 (23.34)	734 (24.39)
Caucasian	1371 (40.23)	499 (25.98)	1036 (37.50)	1084 (36.01)
Hispanic	1200 (35.21)	870 (45.29)	996 (36.50)	1037 (34.45)
Others	148 (4.34)	75 (3.90)	86 (3.11)	155 (5.15)
Age group				
0-3	46 (1.35)	15 (0.78)	21 (0.76)	150 (4.98)
4-8	1348 (39.55)	596 (31.03)	1077 (38.98)	1110 (36.88)
9-12	1362 (39.96)	593 (30.87)	923 (33.41)	911 (30.27)
13-18	652 (19.13)	717 (37.32)	742 (26.85)	839 (27.87)
Mean (± SD)*	9.56 ± 3.20	10.73 ± 3.63	9.92 ± 3.50	9.67 ± 3.98
ENABLING CHARACTERISTICS				
Care-Density				
Mean (± SD)	24.89 ± 31.12	38.16 ± 70.37	34.18 ± 55.94	29.89 ± 44.05
Median (Range)	13.00	8.33	5.67	8.33
NEED CHARACTERISTICS				
Number of mental/behavioral disorders diagnosed				
0	52 (1.53)	1 (0.05)	17 (0.62)	78 (2.59)
1	2174 (63.79)	485 (25.25)	882 (31.92)	1298 (43.12)
2-4	1131 (33.19)	1199 (62.42)	1607 (58.16)	1431 (47.54)
≥5	51 (1.50)	236 (12.29)	257 (9.30)	203 (6.74)
Mean (± SD)	1.53 ± 0.92	2.68 ± 1.49	2.41 ± 1.45	2.06 ± 1.38
Type of mental/behavioral disorder diagnosed				
ADHD	3,121 (91.58)	1431 (74.49)	2329 (84.29)	2188 (72.69)
Bipolar Disorder(s)	111 (3.26)	798 (41.54)	776 (28.09)	560 (18.60)
Depression	200 (5.87)	608 (31.65)	629 (22.77)	549 (18.24)
Anxiety	248 (7.28)	430 (22.38)	529 (19.15)	550 (18.27)
Learning Disorder(s)	357 (10.48)	197 (10.26)	302 (10.93)	427 (14.19)
Adjustment Disorder(s)	255 (7.48)	330 (17.18)	399 (14.44)	354 (11.76)
Conduct Disorder	328 (9.62)	300 (15.62)	440 (15.92)	335 (11.13)

Oppositional Defiant Disorder	195 (5.72)	417 (21.71)	591 (21.39)	378 (12.56)
Schizophrenia	52 (1.53)	213 (11.09)	198 (7.17)	185 (6.15)
Number of prescribers involved in treatment				
2-4	3217 (94.40)	1858 (96.72)	2457 (88.93)	2494 (82.86)
≥5	191 (5.60)	63 (3.28)	306 (11.07)	516 (17.14)
Mean (± SD)	2.62 ± 1.08	2.45 ± 0.83	3.01 ± 1.22	3.28 ± 1.55
Hospitalization/ ER-visit				
Yes	282 (8.27)	613 (31.91)	640 (23.16)	715 (23.75)

Table M2. 2 Demographic and clinical characteristics of patients stratified by receipt of polypharmacy.

Characteristic	Multiple prescribers involved in treatment (N=11,102; 100%)							
	PCPs only		Specialists only		PCP + Specialist		Others	
	Non-polypharmacy (N=3,000; 88.03%)	Psychotropic polypharmacy (N=408; 11.97%)	Non-polypharmacy (N=1,143; 59.50%)	Psychotropic polypharmacy (N=778; 40.50%)	Non-polypharmacy (N=1,578; 57.11%)	Psychotropic polypharmacy (N=1,185; 42.89%)	Non-polypharmacy (N=2,000; 66.45%)	Psychotropic polypharmacy (N=1,010; 33.55%)
PREDISPOSING CHARACTERISTICS								
Sex								
Male	2,064 (68.80)	303 (74.26)	670 (58.67)	465 (59.77)	1,023 (64.83)	781 (65.91)	1219 (60.95)	638 (63.17)
Race								
African American	621 (20.70)	68 (16.67)	286 (25.02)	191 (24.55)	406 (25.73)	239 (20.17)	523 (26.15)	211 (20.89)
Caucasian	1144 (38.13)	227 (55.64)	239 (20.91)	260 (33.42)	452 (28.64)	584 (49.28)	610 (30.50)	474 (46.93)
Hispanic	1095 (36.50)	105 (25.74)	573 (50.13)	297 (38.17)	672 (42.59)	324 (27.34)	750 (37.50)	287 (28.42)
Not reported	140 (4.67)	8 (1.96)	45 (3.94)	30 (3.86)	48 (3.04)	38 (3.21)	117 (5.85)	38 (3.76)
Age group								
0-3	43 (1.43)	3 (0.74)	8 (0.70)	7 (0.90)	10 (0.63)	11 (0.93)	135 (6.75)	15 (1.49)
4-8	1172 (39.07)	176 (43.14)	380 (33.25)	216 (27.76)	625 (39.61)	452 (38.14)	738 (36.90)	372 (36.83)
9-12	1182 (39.40)	180 (44.12)	344 (30.10)	249 (32.01)	516 (32.70)	407 (34.35)	582 (29.10)	329 (32.57)
13-18	603 (20.10)	49 (12.01)	411 (35.96)	306 (39.33)	427 (27.06)	315 (26.58)	545 (27.25)	294 (29.11)
Mean (± SD)*	9.62 ± 3.25	9.14 ± 2.78	10.61 ± 3.66	10.92 ± 3.59	9.96 ± 3.55	9.88 ± 3.43	9.49 ± 4.12	10.05 ± 3.66
ENABLING CHARACTERISTICS								
Care-Density								

Mean (± SD)	25.40 ± 31.90	21.15 ± 24.32	43.90 ± 79.66	29.72 ± 52.83	26.48 ± 51.86	44.43 ± 59.44	31.16 ± 48.24	27.37 ± 34.15
Median	14.00	11.00	9.00	7.42	3.58	11.50	6.33	12.74
NEED CHARACTERISTICS								
Number of mental/behavioral disorders diagnosed								
0	47 (1.57)	5 (1.23)	1 (0.09)	0 (0)	14 (0.89)	3 (0.25)	70 (3.50)	8 (0.79)
1	2002 (66.73)	172 (42.16)	367 (32.11)	118 (15.17)	576 (36.50)	306 (25.82)	1006 (50.30)	292 (28.91)
2-4	922 (30.73)	209 (51.23)	686 (60.02)	513 (65.94)	897 (56.84)	710 (59.92)	866 (43.30)	565 (55.94)
≥5	29 (0.97)	22 (5.39)	89 (7.79)	147 (18.89)	91 (5.77)	166 (14.01)	58 (2.90)	145 (14.36)
Mean (± SD)	1.46 ± 0.84	2.06 ± 1.25	2.37 ± 1.33	3.14 ± 1.59	2.18 ± 1.27	2.71 ± 1.60	1.75 ± 1.12	2.66 ± 1.63
Type of mental/behavioral disorder diagnosed								
ADHD	2731 (91.03)	390 (95.59)	843 (73.75)	588 (75.58)	1298 (82.26)	1031 (87.00)	1,353 (67.65)	835 (82.67)
Bipolar Disorder(s)	79 (2.63)	32 (7.84)	325 (28.43)	473 (60.80)	295 (18.69)	481 (40.59)	188 (9.40)	372 (36.83)
Depression	156 (5.20)	44 (10.78)	317 (27.73)	291 (37.40)	330 (20.91)	299 (25.23)	272 (13.60)	277 (27.43)
Anxiety	185 (6.17)	63 (15.44)	214 (18.72)	216 (27.76)	276 (17.49)	253 (21.35)	315 (15.75)	235 (23.27)
Learning Disorder(s)	308 (10.27)	49 (12.01)	126 (11.02)	71 (9.13)	190 (12.04)	112 (9.45)	330 (16.50)	97 (9.60)
Adjustment Disorder(s)	218 (7.27)	37 (9.07)	186 (16.27)	144 (18.51)	207 (13.12)	192 (16.20)	211 (10.55)	143 (14.16)
Conduct Disorder	275 (9.17)	53 (12.99)	166 (14.52)	134 (17.22)	250 (15.84)	190 (16.03)	190 (9.50)	145 (14.36)
Oppositional Defiant Disorder	120 (4.00)	75 (18.38)	219 (19.16)	198 (25.45)	296 (18.76)	295 (24.89)	193 (9.65)	185 (18.32)
Schizophrenia	35 (1.17)	17 (4.17)	86 (7.52)	127 (16.32)	81 (5.13)	117 (9.87)	67 (3.35)	118 (11.68)
Number of prescribers involved in treatment								
2-4	2841 (94.70)	376 (92.16)	1126 (98.51)	732 (94.09)	1,479 (93.73)	978 (82.53)	1800 (90.00)	694 (68.71)
≥5	159 (5.30)	32 (7.84)	17 (1.49)	46 (5.91)	99 (6.27)	207 (17.47)	200 (10.00)	316 (31.29)

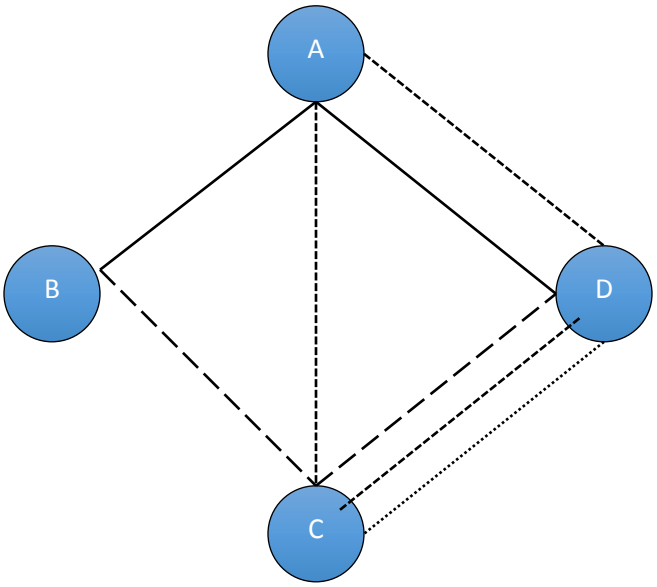
Mean (± SD)	2.59 ± 1.03	2.84 ± 1.38	2.29 ± 0.63	2.67 ± 1.03	2.73 ± 1.02	3.40 ± 1.34	2.92 ± 1.22	3.98 ± 1.87
Hospitalization/ ER-visit								
Yes	238 (7.93)	44 (10.78)	297 (25.98)	316 (40.62)	290 (18.38)	350 (29.54)	380 (19.00)	335 (33.17)

Table M2. 3 Multivariate logistic regression model by study groups.

Characteristic	PCPs only			Specialists only			PCP + Specialist			Others		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
ENABLING CHARACTERISTICS												
Care-Density (Ref: less than 100)												
Care-Density (Higher than median)	0.722	0.618-0.963	0.022	0.930	0.752-1.149	0.499	2.006	1.680-2.397	<0.001	1.295	1.073-1.563	0.007
PREDISPOSING CHARACTERISTICS												
Age												
Age	0.963	0.928-1.000	0.050	1.005	0.971-1.041	0.780	0.966	0.938-0.994	0.018	0.993	0.966-1.020	0.605
Sex (Ref: Female)												
Male	1.464	1.135-1.889	0.003	1.169	0.935-1.463	0.171	1.174	0.975-1.415	0.091	1.131	0.933-1.371	0.210
Race (Ref: African American)												
Caucasian	1.817	1.339-2.464	<0.001	1.479	1.114-1.964	0.007	2.190	1.754-2.733	<0.001	1.751	1.397-2.194	<0.001
Hispanic	0.926	0.661-1.298	0.656	0.798	0.617-1.033	0.087	0.889	0.706-1.119	0.317	1.049	0.823-1.337	0.701
Not reported	0.567	0.259-1.241	0.156	1.017	0.591-1.752	0.951	1.600	0.979-2.615	0.061	1.368	0.873-2.142	0.171
NEED CHARACTERISTICS												
Number of mental/behavioral disorders diagnosed												
No. of MHD	1.884	1.383-2.565	<0.001	0.911	0.699-1.186	0.488	1.346	1.053-1.719	0.018	1.232	0.975-1.557	0.081
Type of mental/behavioral disorder diagnosed (Ref: No)												
ADHD	1.781	0.954-3.326	0.070	2.487	1.673-3.695	<0.001	1.334	0.929-1.918	0.119	2.421	1.736-3.377	<0.001

Bipolar Disorder(s)	1.508	0.847-2.684	0.163	4.360	3.036-6.261	<0.001	2.117	1.522-2.945	<0.001	3.489	2.483-4.902	<0.001
Depression	1.059	0.612-1.832	0.838	1.588	1.068-2.361	0.022	0.891	0.620-1.278	0.529	1.594	1.102-2.306	0.013
Anxiety	1.431	0.877-2.334	0.151	1.632	1.110-2.401	0.013	1.001	0.709-1.414	0.994	1.066	0.749-1.518	0.723
Learning Disorder(s)	0.423	0.256-0.700	<0.001	1.165	0.743-1.828	0.505	0.513	0.349-0.753	<0.001	0.558	0.375-0.831	0.004
Adjustment Disorder(s)	0.394	0.230-0.677	<0.001	1.039	0.715-1.508	0.842	0.677	0.474-0.968	0.032	0.759	0.521-1.104	0.149
Conduct Disorder	0.547	0.336-0.890	0.015	0.945	0.626-1.428	0.789	0.597	0.420-0.849	0.004	0.831	0.567-1.219	0.345
Oppositional Defiant Disorder	2.127	1.329-3.403	0.002	1.200	0.825-1.746	0.341	0.814	0.584-1.136	0.227	1.002	0.703 1.428	0.992
Schizophrenia	1.776	0.856-3.684	0.123	1.657	1.071-2.563	0.023	0.995	0.636-1.557	0.982	1.682	1.053-2.687	0.030
Hospitalization/ER visit (Ref: No)												
Yes	1.084	0.743-1.581	0.677	0.946	0.713-1.255	0.702	1.124	0.894-1.414	0.316	1.054	0.831-1.337	0.664
Number of prescribers involved in treatment												
No. of Prescribers	1.120	1.024-1.226	0.014	1.676	1.461-1.922	<0.001	1.395	1.290-1.509	<0.001	1.447	1.360-1.540	<0.001

Figure M2. 1 PCN for understanding Care Density



An example of care density is illustrated in Figure M2.1. In this figure, there are four providers represented by circles (labeled A through D) and 4 patients represented by different line styles (solid, dotted, long dashed, and short dashed). Care density equals the sum of the number of shared patients among a patient's providers divided by the total number of provider pairs that a patient sees. For example, the patient represented by the dotted line sees providers C and D. The numerator of care density is the 3 patients shared by these doctors. The denominator is 1 for 1 pair of doctors. Thus, the patient represented by the solid line has a care density of 3 divided by 1 or 3. The patient represented by the long dashed line sees providers B, C, and D. Provider pair B and D share 0 patients, pair B and C share 1, and pair C and D share 3. The numerator is 4. The denominator is 3 pairs of doctors. Care density for the patient represented by the long dashed line is 4 divided by 3 or 1.33.

MANUSCRIPT 3

Physician Peer-influence on Prescribing Psychotropic Polypharmacy in the Treatment of Children and Adolescents with Mental Disorders

Abstract

BACKGROUND: Prescription of psychotropic polypharmacy in the management of pediatric mental disorders is on the rise. Studies have shown that, physicians' prescribing behaviors can be influenced by their peers, however no study has yet examined the relationship between physician peer-influence and prescription of psychotropic polypharmacy.

OBJECTIVE: To examine the effect of physician peer-influence on the prescription of psychotropic polypharmacy among children and adolescents treated for mental/behavioral disorders.

METHODS: A retrospective cross-sectional study was conducted using the 2013-2015 administrative claims data from Texas Children's Health Plan (TCHP). The study included individuals: a) ≤18 years of age, b) diagnosed with a mental disorder, and c) received psychotropic prescriptions from a single prescriber during the study period. The outcome of interest was psychotropic polypharmacy, defined as the receipt of ≥ 2 psychotropic medications from different drug classes concurrently for 60 days or more. Multilevel generalized linear mixed models (GLIMMIX) was used to study the association between prescriber-level social network influence measures (created using patient-sharing relationships between physicians) and patient-level risks of receiving psychotropic polypharmacy by adjusting for the practice-level (practice size, type of practice), physician-level (peer-influence measures, gender and specialty) and patient-level (patient age, gender, race; number of mental/behavioral disorders diagnosed; type of mental/behavioral disorder diagnosed; and whether a specialist was involved in treatment) covariates.

RESULTS: A total of 24,147 children and adolescents were diagnosed with a mental disorder and had received at least one psychotropic medication. Of these, nearly half (n=13,045; 54.02%)

met the study inclusion criteria. The multilevel models found that as a physician is exposed more to their peers prescribing polypharmacy through sharing of same patients, there is 77% higher likelihood of receiving psychotropic polypharmacy (OR=1.766; 95% CI 1.027-3.037); similarly, as physicians occupy more similar position in patient-sharing network, there is almost 4-times higher likelihood of receiving psychotropic polypharmacy (OR=4.236; 95% CI 2.071-8.666). Other than these physician-level peer influence measures, physician specialty and patient-level factors including gender, race and diagnosis of attention-deficit/hyperactivity disorder, bipolar disorder and depression were associated with prescription of psychotropic polypharmacy.

CONCLUSIONS: Physician peer-influence was strongly associated with the prescription of psychotropic polypharmacy. Our study implies that targeting and changing the prescribing behaviors of guideline non-concordant physicians would be useful to enhance the diffusion of guideline concordant practices among other physicians.

INTRODUCTION

The use of psychotropic polypharmacy (combination of psychotropic medications) to treat mental/behavioral disorders is on the rise among children and adolescents despite the recommendations of the clinical guidelines[1] to use monotherapy in this population. The overall prevalence of psychotropic polypharmacy in the US pediatric population ranges from 14% to 73% [2-9], which is alarming given the number of health concerns associated with it, such as adverse events[10,11], drug-drug interactions[12,13], non-adherence[14], higher-healthcare costs[15], morbidity and mortality[16,17]. There is only limited scientific evidence for understanding the immediate or long-term effects of polypharmacy on the child's growth and development, making it an important public health concern.[18]

Due to the growing concerns, many of the State Medicaid agencies throughout the US have introduced programs to monitor the prescribing of psychotropic medications in children and adolescents.[19] One such program that has led to a significant reduction in the instances of psychotropic polypharmacy in the foster care population in the state of Texas is the Psychotropic Medication Utilization Review (PMUR) program.[20] The existing PMUR process views guideline non-concordant prescribing (especially polypharmacy) as the outcome of individual physicians' knowledge and attitude. The whole emphasis of these programs is on the non-concordant behavior of a single individual physician. However, these programs fail to consider the effect of the environment from which such behavior might have originated. Specifically, the effect of physician peer-influence on the prescribing practices is not accounted by these programs. During the provision of care, physicians interact with multiple other physicians either within the organization or outside of it, forming social and professional relationships with their peers. Physicians seldom work as isolated individuals, they are a part of a social structure where they

exert influence on each other as a result of day-to-day interactions, referrals and sharing of patients.[21] Most of the times peer-influence shapes the practice behaviors of the physicians. Clusters of physicians usually adopt the behavior of their peers and opinion leaders (most influential physicians) during the provision of care. Previous studies have shown that, physicians' prescribing behavior can be influenced by their peers in addition to their own personal preferences.[22, 23, 24]

In the context of psychiatric care and prescription of psychotropic medications it can be theorized that, if there is a strong effect of physicians' peers in the prescribing of psychotropic medications, targeting and changing the prescribing behaviors of guideline non-concordant (polypharmacy) physicians could lead to a cascading effect in guideline diffusion among other physicians within the social structure, resulting in increased concordance with guidelines. Thus, it is very important to examine if there is peer-influence on the prescribing practices of physicians prescribing psychotropic medications to children and adolescents with mental disorders. In order to examine the physician peer-influence in the current study we developed physician patient-sharing networks using the administrative claims data from Texas Children's Health Plan and applied the concepts and techniques of Social Network Analysis (SNA).

Social Network Analysis is a set of theories and techniques used to understand how social relationships (e.g., friendship, advice seeking, and discussion) influence behaviors.[25-28] SNA is commonly used to study relationships between individuals and communities as they interact with each other. In the healthcare domain, social network analysis has been used to analyze health care networks, addressing topics such as the exchange of clinical advice, the diffusion of new pharmaceuticals, or organizational performance and cost-efficiency.[23, 24, 29, 30] The studies on diffusion of new pharmaceuticals have used SNA to analyze the influence of opinion leaders or

key action leaders on daily prescribing practices.[24] SNA can help examine physicians' behaviors in the context of their professional social structure (network) where they communicate, collaborate, compete and exert influences on each other. SNA provides a unique perspective to understand the underlying reasons of prescribing decisions and medication errors.

The objective of this study was to examine the effect of physician peer-influence on the prescribing of psychotropic polypharmacy among children and adolescents treated for mental/behavioral disorders. The measures of social network analysis that were used to examine the peer-influence were affiliation-based peer influence (exposure through sharing same patients) and network influence based on structural equivalence (exposure through occupying similar network position). A multilevel statistical analysis was conducted to model the association between these network influence measures and prescription behavior, controlling for the clinic level, physician level and patient level factors that might be associated with psychotropic polypharmacy.

METHODS

Study Design and Data Source:

A retrospective cross-sectional study was conducted using the administrative claims data from Texas Children's Health Plan (TCHP) for the period of July 1, 2013 to June 30, 2015. Data was obtained for children and adolescents who were ever diagnosed with mental/behavioral disorders identified using ICD 9-CM codes (Appendix A) and who had continuous enrollment throughout the study period. TCHP is the nation's first health maintenance organization (HMO) created just for children. It is an administrator for the State Children's Health Insurance Program (CHIP) and STAR/Medicaid managed care programs through a contract with the state Medicaid administrator. TCHP has more than 400,000 members and over 1,100 primary care physicians,

3,200 specialists and 60 hospitals that provide service and patient care to these members. Of the 400,000 members 68% are Hispanics, 16% are Caucasians, 9% are African Americans and the rest are other racial/ethnic groups. TCHP data contains information on outpatient medical claims, and pharmacy claims. It also provides information on the physician that was involved in the care/treatment during each patient visit (claim) such as the physician ID, gender, and specialty. Additionally, the data includes information on patient characteristics e.g. patient age, gender, and race. The data is de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) standards.

Study Sample:

The study included individuals who: a) were 0 to 18 years of age (children and adolescents), b) were diagnosed with a mental/behavioral disorder, c) had at least one pharmacy claim of psychotropic medication, and d) received prescription for psychotropic medication from single prescriber throughout the study period. Further, these individuals were required to be continuously enrolled in the Texas Children Health Plan. Individuals who received prescription of psychotropic medication from multiple prescribers during the study period were excluded from the study. The psychotropic medications considered in the study included: medications for attention-deficit hyperactivity disorder such as stimulants, non-stimulant (atomoxetine), alpha-agonists (guanfacine, clonidine); anti-depressant medications (selective serotonin norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and tricyclic antidepressants); antipsychotic agents (first and second generation); lithium; anticonvulsant mood-stabilizers (such as divalproex, oxcarbazepine, carbamazepine, lamotrigine), and anxiolytics (such as hydroxyzine and benzodiazepines).

Two-mode network data and Peer-influence Measures: [31, 32]

This study measured physician peer-influence based on co-membership in events (sharing of patients). We assumed that sharing of patients increases the probability of forming professional relationships among physicians. The two-mode network data was used to operationalize the peer-influence measures. In the two-mode network data, structural variables are measured on two set of nodes. In case of this study, the first mode is a set of physicians within the Texas Children's Health Plan caring for mental/behavioral health patients and the second mode is the set of patients to whom the physicians in the first set prescribed psychotropic medications. Such a network is called as the affiliation network with each physician (indexed in row), with each patient (indexed in column) in the N×K matrix A, with each entry in the matrix A equal to 1 if the physician (row actor) prescribed psychotropic medication to the patient (column event), and 0 otherwise. Two measures of peer-influence were used in this study 1) affiliation exposure (representing cohesion) and 2) structural equivalence exposure (representing similarity). Cohesion represents the direct connection between the peers in a network. It indicates that the individual has ties with other individuals within the network who can influence that individual through frequent and direct communication.[32, 33] On the other hand, structural equivalence represents "the degree of similarity of actor network profiles in which two individuals are considered proximate to the extent that they have the same pattern of interpersonal relations with others". [32, 34] Historically network measures of cohesion and structural equivalence have been used to study the diffusion of pharmaceutical prescription behaviors of physicians. The effect of cohesion on the diffusion of tetracycline prescription behaviors of physicians has been studied previously by Coleman and colleagues[35] which was later reanalyzed by Burt[34] to study the effect of structural equivalence on diffusion of tetracycline and to differentiate it from cohesion based influence.

Affiliation Exposure (AE):

We used the affiliation exposure model (Fujimoto et al., 2011; Fujimoto et al., 2012) to measure the extent to which a physician is exposed to the polypharmacy prescribing behavior of other physicians via sharing of patients. It was computed using the affiliation matrix A, in which the rows indexed individual physicians, and the columns indexed all the patients with mental/behavioral disorders. This affiliation matrix was then multiplied by its transpose to create a one-mode physician-by-physician co-participation matrix, C, where each off-diagonal entry represents the number of patients shared between the physician pair, and on-diagonal entry represents the number of patients each physician had. The co-participation matrix, C, was then row-normalized by dividing each entry by the row total of the C matrix to ensure that the entry values range from 0 to 1, but the diagonal entries were suppressed by setting them to zero (but in a regression analysis, it was used as one of the controlled variables). Finally, the normalized co-participation matrix, C, was multiplied by the vector representing the polypharmacy prescribing behavior of each alter. The resulting vector is the affiliation exposure vector that represents the level of being exposure to the polypharmacy prescribing behavior of other physicians with whom they shared patients (ranging from 0 to 1).

Structural Equivalence Exposure (SE):

The calculation of Structural Equivalence Exposure was computed using a one-mode physician-by-physician co-participation matrix, C, to compute the structural equivalence matrix S (diagonal values were ignored) developed by calculating the Pearson correlation for all non-adjacent actors. This structural equivalence matrix S was then row-normalized by dividing each entry by the row total of the S matrix. Finally, the normalized structural equivalence matrix, S,

was multiplied by the vector representing the polypharmacy prescribing behavior of each alter. The resulting vector was the structural equivalence exposure vector (H).

The structural equivalence exposure measures the degree to which an actor (physician) is exposed to the behavior (polypharmacy prescribing behaviors) of their structurally equivalent peers. Social influence based on structural equivalence puts emphasis on the competition/comparison between ego and alter[31, 34]. We assumed that the more similar two people are in the network, the more substitutable they are and may lead to increased feelings of competition. People who occupy similar structural positions (in terms of patterns of relations with all other actors in the network) will influence each other.

Physician Specialty:

Physicians were classified as a) Primary Care Physicians (PCPs) (e.g. general medicine, family medicine, and internal medicine), b) Specialists (e.g. psychiatry, addiction medicine, and psychosomatic medicine), c) Others (all other than PCP and specialist) based on the physician specialty reported in the data. For those physicians with missing values for specialty, the information was obtained from the National Plan and Provider Enumeration System (NPPES), National Provider Identifier (NPI) database using the NPI number for the physicians reported in the TCHP data.

Practice Setting:

The NPPES NPI database was used to obtain the location of practice for each of the physicians in this study, as the TCHP data had information missing for many of the physicians. Practice locations' addresses were converted into geocodes (longitude and latitude coordinates). If the geocodes for physicians matched exactly, then the physicians were considered as belonging to the same practice, this algorithm has been previously validated by Miller et al[36]

(2014). Depending on the specialty of the physicians practicing in these practice settings (clinics) the practice settings were classified as a) PCP only, b) Specialist only, c) Others (non-PCP, non-specialist) and d) Mix (PCPs, specialists and others all in one practice location).

Outcome Measure:

The outcome of interest was whether an individual had at least one episode of multiclass psychotropic polypharmacy during the study period, measured as a binary variable (1: Yes, 0: No). An episode of multiclass psychotropic polypharmacy was defined as the receipt of ≥ 2 psychotropic medications from different drug classes concurrently for 60 days or more, with no gaps in polypharmacy treatment. The 60-day overlap criterion is the most commonly implemented cutoff used to define polypharmacy, it avoids misclassifying instances of cross-titration as polypharmacy.[37, 38] Patients who received psychotropic medications but did not have a polypharmacy episode at any time during the study period were classified as non-polypharmacy cases. Episodes of treatment were identified using the prescription fill date and the days' supply information available from the pharmacy claims. Before measuring the episodes, overlapping days' supply for the same medication were carried forward assuming that the patient finished the current prescription before starting on the refill prescription. Gaps in fills of the same medication of ≤ 15 days were allowed and adjusted in the calculation of the overlap. Further, the overlap was defined by drug class and not specific medications within class, so it was not necessary for a single medication within a class to overlap by ≥ 60 days with a particular medication in another class. Only unique combinations of drug classes of at least 60 days were considered.

Statistical Analysis:

Descriptive statistics, including frequencies and mean (± SD) were used to characterize patients' demographic and clinical characteristics, physician characteristics and practice (clinic) characteristics. The differences between patient groups (polypharmacy/non-polypharmacy) were analyzed using t-tests and Chi-square tests. A-priori significance level of $p<0.05$ was chosen for all comparisons.

Multilevel generalized linear mixed models (GLIMMIX) with log link function was applied to test the association between prescriber-level peer-influence measures (affiliation exposure, structural equivalence) and patient-level risks of receiving multi-class psychotropic polypharmacy (dependent variable). The data was structured as patients nested under prescribers nested within each practice. A three-level hierarchical analysis that accounts for the nesting effect allowed to test for significant prescriber-level effects while controlling for patient-level covariates and practice-level clustering. In addition to the main independent variables (network measures for peer influence), the 3-level GLIMMIXs also adjusted for practice level covariates (practice size, type of practice), prescriber level covariates (gender and specialty), and patient level covariates (patient age, gender, race; number of mental/behavioral disorders diagnosed; type of mental/behavioral disorder diagnosed; and whether a specialist was involved in treatment). Two separate GLIMMIX models were conducted, one for affiliation exposure and the other for structural equivalence exposure. Network measures were calculated using UCINET 6 software (Analytic Technologies, Harvard, MA) and Microsoft Excel software. All statistical analyses were conducted by using SAS 9.3 software (SAS Institute, Inc, Cary, NC).
The study was reviewed and approved by the University of Houston Institutional Review Board.

RESULTS

Patient level descriptive statistics:

A total of 24,147 children and adolescents were diagnosed with a mental/behavioral disorder and had at least one pharmacy claim of psychotropic medication during the study period. Of these 13,045 (54.02%), individuals were prescribed psychotropic medications by single prescriber throughout the study period. The demographic and clinical characteristics of the children and adolescents on psychotropic medications, along with the unadjusted results of differences between the non-polypharmacy and the polypharmacy groups are provided in Table M3.1. Majority of the patients in both non-polypharmacy and polypharmacy group were male, 62.38% and 66.73% respectively. Non-polypharmacy patients were predominantly Hispanic (46.35%), while patients experiencing psychotropic polypharmacy were predominantly Caucasian (38.10%). The mean age of patients was higher in the polypharmacy group as compared to the non-polypharmacy group (10.15 ± 3.46 vs. 9.66 ± 4.07, $p<0.001$). Higher proportion of patients experiencing psychotropic polypharmacy were diagnosed with multiple mental/behavioral disorders compared to non-polypharmacy cases (60.34% vs. 38%, $p<0.001$). The most common diagnosis among both polypharmacy and non-polypharmacy groups was attention-deficit hyperactivity disorder, with polypharmacy group having a substantially higher proportion (84.42% vs. 66.42%, $p<0.001$). Diagnosis of bipolar disorder(s) was almost four times higher among the patients experiencing psychotropic polypharmacy as compared to non-polypharmacy patients (30.34% vs. 8.24%, $p<0.001$). A higher proportion of patients who experienced psychotropic polypharmacy were diagnosed with depression (16.67% vs. 11.36%, $p<0.001$) and schizophrenia (4.29% vs. 2.57%, $p<0.001$) as compared to the non-polypharmacy patients. On the other hand, a lower proportion of patients experiencing psychotropic polypharmacy were diagnosed with learning disorder(s) compared to the non-polypharmacy group (8.71% vs. 14.76%, $p<0.001$). A substantially higher proportion of patients experiencing

psychotropic polypharmacy had a specialist involved in the treatment (79.73% vs. 35.78%, $p<0.001$) as compared to those patients who were identified as non-polypharmacy.

About 74% of the patients experiencing polypharmacy were prescribed medications by a male physician as compared to about 54% of non-polypharmacy patients ($p<0.001$). A comparatively higher proportion of patients experiencing polypharmacy were provided treatment by a specialist throughout the study period as compared to the non-polypharmacy patients (76.04% vs. 35.64%).

Physician and Practice level descriptive statistics:

Table M3.2 presents the physician and practice setting characteristics. Most of the physicians in the patient-sharing network were females (52.95%) and primary care physicians (61.42%). Among all type of practice settings, the practices with PCPs only were the most common (57.79%), followed by others (19.30%), Specialist only (13.88%) and Mix (9.03%). The average number of physicians per setting was 1.86 (±3.52).

Physician peer-influence measures:

The average affiliation exposure for the physicians in this patient-sharing network was 0.29 ± 0.31 (median= 0.21, range= 0-1) and the average structural equivalence exposure in this patient sharing network was 0.15 ± 0.53 (median= 0.22, range= -15.93-2.05).

Multilevel Logistic Regression model:

Table M3.3 and Table M3.4 summarize the results of the multilevel logistic regression model for affiliation exposure and structural equivalence exposure respectively.

Practice level factors:

The multilevel models showed that there was significant variation in the likelihood of receiving psychotropic polypharmacy across different practice settings. Statistics showed that

about 34% of the variation in the receipt of psychotropic polypharmacy was explained by the practice settings, leaving the rest to be explained by physicians, patient related factors or other factors. However, practice size and type of practice were not significantly associated with the receipt of psychotropic polypharmacy in both the models.

Physician level factors:

Each unit increase in affiliation exposure from the mean was associated with 77% higher likelihood of receiving psychotropic polypharmacy (OR=1.766; 95% CI 1.027-3.037) which implies that having more patient sharing relationship with a polypharmacy prescriber was associated with a physician's prescribing behavior (Table M3.3). In case of structural equivalence exposure, each unit increase from the mean was associated with almost 4-times higher likelihood of receiving psychotropic polypharmacy (OR=4.236; 95% CI 2.071-8.666). This indicates that, more similar the position of a pair of physicians in a physician patient-sharing network, expressed as their relationship with all other physicians within the network, the more likely they will have similar behavior in terms of prescribing psychotropic polypharmacy (Table M3.4).

Other than the physician-level peer-influence measures, physician specialty was significantly associated with the receipt of psychotropic polypharmacy among patients with mental/behavioral disorders. Patients treated by specialists throughout the study period had about 3 times higher likelihood of receiving psychotropic polypharmacy as compared to patients treated by primary care physicians (AE model: OR=3.627; 95% CI 2.174-6.053 and SE model: OR=3.532; 95% CI 2.113-5.904). Physician gender was not significantly associated with the receipt of polypharmacy among patients.

Patient level factors:

The odds ratios and confidence intervals for the patient level factors for AE model and SE model are presented in Table M3.3 and Table M3.4 respectively. Males had a 14% higher likelihood of experiencing psychotropic polypharmacy compared to females. As compared to African Americans, Caucasians were 63% more likely to experience polypharmacy while Hispanics were 25% less likely to experience polypharmacy. Patients diagnosed with ADHD, bipolar disorder(s) and depression had 2.5 times, 2.7 times and 1.3 times higher likelihood of experiencing polypharmacy respectively, while patients diagnosed with adjustment disorder(s) were 25% less likely to experience psychotropic polypharmacy.

DISCUSSION

This is the first study to examine the effects of affiliation exposure (through sharing common patients) and structural equivalence exposure (occupying similar position in patients-sharing network), as measures of peer-influence, on the prescribing behaviors of physicians, resulting in the receipt of psychotropic polypharmacy in children and adolescents with mental/behavioral disorders. A positive relationship was observed between affiliation exposure and the probability of receiving psychotropic polypharmacy. Results showed that physicians who are exposed to the polypharmacy prescribing behavior of other physicians via direct patient-sharing ties are more likely to prescribe psychotropic polypharmacy. The higher the extent of exposure to polypharmacy prescribing behavior of direct ties, higher is the likelihood of prescribing polypharmacy. Previous studies have shown that physicians who share greater number of patients communicate with each other and tend to have stronger collaborative relationships. A study by Barnett et al validated that physicians who shared 8 or more patients had 80% probability of having an information-sharing relationship.[30] Physician peers having direct ties communicate with each other regarding the diagnostic and treatment practices that

they implement in their patient panel. Thus, polypharmacy prescribing behavior of one physician can be adopted by the other physician peers in such direct patient-sharing ties.

It was found that structural equivalence exposure had a stronger association with psychotropic polypharmacy than the affiliation exposure. The reason for this may be that, affiliation resulting from sharing of patients might not necessarily represent direct communication between the physicians. Many times physicians' share patients with each other but do not come in direct contact. For example, with the advent of electronic medical records, the patient's diagnosis, treatment and care history directly reaches other physician with whom the patient is shared, but there is no direct communication between the two physicians.

Structural equivalence exposure was the single most prominent factor associated with the receipt of psychotropic polypharmacy even after controlling for practice-level, physician-level and patient-level covariates. Structural equivalence is driven by social comparison such as imitation or competition between the ego and alter.[39] Usually, exact match of structural equivalence is rare in a large network of physicians thus the degree of structural equivalence is measured to approximate equivalence. According to Burt (1982) [40] "structural equivalence predicts that two people identically positioned in the flow of influential communication will use each other as a frame of reference for subjective judgments and so make similar judgments even if they have no direct communication with each other". Structurally equivalent actors have same structural characteristics and are identically positioned in the network, making them substitutable. As a result, structurally equivalent actors use one another to evaluate each other's beliefs, attitudes and behaviors.[32] In context of the current study, structurally equivalent physicians occupy the same position in the social structure and proximate a pattern of relations with other physicians in the network. According to the social network theory, the more similar

two physicians' relations with other physicians are, that is, the more one physician could substitute for another physician in his/her role or relations, the more intense the physician's feeling of competition with the other. These competing physicians tend to use one another to evaluate their relative adequacy. It is likely that if one of the physician in the structurally equivalent pair prescribes psychotropic polypharmacy to treat his/her patients in order to achieve desired outcomes, the other physician will imitate the behavior either through sense of competition or comparison to achieve similar outcome in his/her patient panel. Additionally, in case of lower density networks structural equivalence may be the only source of diffusion as the ties between the directly connected actors are not dense (strong) enough for direct influence through affiliation.[39]

In addition to the network measures of peer-influence, there were practice-level, physician-level and patient-level factors that were strongly associated with the receipt of psychotropic polypharmacy among children and adolescents with mental/behavioral disorders. The likelihood of receiving psychotropic polypharmacy differed across practice settings, however the size and type of practice was not significantly associated with psychotropic polypharmacy. It is possible that the variation in the likelihood of receiving polypharmacy could have been observed due to differing organizational structures, processes of care and policies implemented in these practices. Findings suggest physician related differences in the likelihood of receiving psychotropic polypharmacy, especially the likelihood of experiencing psychotropic polypharmacy varied based on the specialty of the physician involved in the treatment. Children and adolescents who were prescribed psychotropic medications by specialists (psychiatrists) throughout the study period had a significantly higher probability of experiencing psychotropic polypharmacy as compared to those who were treated by primary care physicians. This finding

is consistent with the previous literature. The probable reason for this might be that specialists have advanced training in the care and treatment of psychiatric disorder, thus are more comfortable prescribing psychotropic medications than the primary care physicians.[41] Other reason according to literature is that psychiatrists heavily emphasize on symptom reduction rather than the disorder itself leading to prescription of more medications.[42-44]

Patient demographics and clinical characteristics were among the most dominant risk-factors associated with the receipt of psychotropic polypharmacy. Male patients had a higher likelihood of receiving psychotropic polypharmacy. Caucasians had a higher likelihood of receiving psychotropic polypharmacy while Hispanics were less likely to experience polypharmacy, which might be due to the differences in the care seeking behaviors of these racial groups. Caucasians tend to discuss their symptoms and seek treatment options while Hispanics are less accepting of treatment for mental/behavioral disorders.[45] As expected and consistent with the literature, co-occurring mental/behavioral disorders were among the strongest predictors of polypharmacy, specifically ADHD, bipolar disorder(s) and depression. In some instances these disorders may lead to clinical complexity in patients justifying the need for use of psychotropic polypharmacy. However, appropriate follow-up and monitoring of these patients is all the more important to make sure that psychotropic polypharmacy is effective in reducing symptoms and not leading to unwanted side effects.

There were several limitations to this study. First, this was a cross-sectional study thus only association between the peer-influence measures and psychotropic polypharmacy could be observed. Longitudinal relationships and change in exposure over time could not be accounted for. Second, the structural dimensions of the overall network structure such as network density, or that of individuals such as centrality was not measured. Third, the network measures of peer-

influence were calculated using the administrative claims data based on the assumption that physicians who share patients are connected with each other and have direct ties, however it might not be necessarily true as patients might visit two different physicians without direct communication between those physicians. Lastly, clinical severity of the patient could not be assessed using the claims data.

CONCLUSIONS

This study found that physician peer-influence was strongly associated with the prescription of psychotropic polypharmacy. Specifically, peer-influence was observed between physicians having direct ties with other physicians through patient-sharing and among those physicians who occupied similar structural positions within the physician network. The greater the extent of exposure to the polypharmacy prescribing behavior of direct ties, greater was the likelihood of polypharmacy. Additionally, more similar the physician's pattern of relations with all other physicians in the network who ever prescribed polypharmacy the higher was the likelihood of polypharmacy. Further, differences were observed in the likelihood of receiving psychotropic polypharmacy across different practice settings, physician specialties and patient's clinical characteristics. The findings support the hypothesis that targeting and changing the prescribing behaviors of guideline non-concordant physicians can lead to diffusion of guideline concordant practices among other physicians.

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Table M3. 1 Demographic and clinical characteristics

Characteristic	Single prescriber involved in treatment (N=13,045; 100%)	
	Non-polypharmacy (N=11,575; 88.73%)	Psychotropic polypharmacy (N=1,470; 11.27%)
Patient Gender		
Male	7220 (62.38)	981 (66.73)
Race*		
African American	2733 (23.61)	411 (27.96)
Alaskan	27 (0.23)	5 (0.34)
Asian	175 (1.51)	7 (0.48)
Caucasian	2908 (25.13)	560 (38.10)
Hispanic	5364 (46.35)	452 (30.75)
Not reported	367 (3.17)	35 (2.38)
Age group*		
0-3	691 (5.97)	8 (0.54)
4-8	4197 (36.26)	548 (37.28)
9-12	3455 (29.85)	500 (34.01)
13-18	3232 (27.92)	414 (28.16)
Mean (± SD)*	9.66 (4.07)	10.15 (3.46)
Number of mental/behavioral disorders diagnosed*		
0	562 (4.86)	12 (0.82)
1	6615 (57.15)	571 (38.84)
2-4	4214 (36.41)	814 (55.37)
≥5	184 (1.59)	73 (4.97)
Mean (± SD)*	1.56 (0.99)	2.10 (1.23)
Type of mental/behavioral disorder diagnosed		
ADHD*	7688 (66.42)	1241 (84.42)
Bipolar Disorder(s)*	954 (8.24)	446 (30.34)
Depression*	1315 (11.36)	245 (16.67)
Anxiety*	1308 (11.30)	217 (14.76)
Learning Disorder(s)*	1708 (14.76)	128 (8.71)
Adjustment Disorder(s)	1112 (9.61)	134 (9.12)
Conduct Disorder	1144 (9.88)	202 (13.74)
Oppositional Defiant Disorder	832 (7.19)	220 (14.97)
Schizophrenia	297 (2.57)	63 (4.29)
Hospitalization/ ER-visit*		
Yes	1103 (9.53)	202 (13.74)
Specialist visited		
Yes*	4142 (35.78)	1172 (79.73)
Physician Gender		
Male	6181 (54.18)	1208 (74.20)
Physician Specialty		
Specialist	4066 (35.64)	1238 (76.04)
Primary Care Physicians	6272 (54.97)	354 (21.74)

Others	1071 (9.39)	36 (2.21)
	Type of Practice	
Specialist only	2961 (25.95)	993 (61.00)
Primary Care Physicians only	5116 (44.84)	303 (18.61)
Mix	2924 (25.63)	320 (19.66)
Others	408 (3.58)	12 (0.74)

Table M3. 2 Physician and Practice setting characteristics

Characteristic	N (%)
Physician Gender	
Male	733 (47.05)
Female	825 (52.95)
Physician Specialty	
Specialist	219 (14.06)
Primary Care Physicians	957 (61.42)
Others	382 (24.52)
Practice Type	
Specialist Only	123 (13.88)
Primary Care Physicians Only	512 (57.79)
Mix	80 (9.03)
Others	171 (19.30)
Practice Size	
Mean (± SD)	1.86 (±3.52)

Table M3. 3 Multilevel Logistic Regression model to determine the association between affiliation exposure and psychotropic polypharmacy

Characteristic	OR	95% CI	p
PRACTICE CHARACTERISTICS			
Practice Size	0.999	0.969-1.030	0.957
Type of Practice (Ref: Primary Care only)			
Specialists only	1.687	0.859-3.311	0.129
Mix	1.073	0.599-1.922	0.813
Others only	0.715	0.249-2.054	0.534
PHYSICIAN CHARACTERISTICS			
Affiliation Exposure	1.766	1.027-3.037	0.040
Physician Specialty (Ref: Primary Care)			
Specialist	3.627	2.174-6.053	<0.001
Others	1.232	0.635-2.388	0.537
Physician Gender (Ref: Female)			
Male	1.272	1.024-1.581	0.039
PATIENT CHARACTERISTICS			
Patient age	0.997	0.979-1.015	0.718
Number of mental/behavioral disorders diagnosed	1.066	0.885-1.285	0.501
Patient Gender (Ref: Female)			
Male	1.147	1.007-1.307	0.030
Patient Race (Ref: African American)			
Alaskan/American Indian	1.575	0.498-4.981	0.440
Asian/pacific	0.306	0.134-0.701	0.005
Caucasian	1.639	1.395-1.926	<0.001
Hispanic	0.748	0.635-0.881	<0.001
No ethnicity	1.405	0.942-2.097	0.095
Mental/behavioral Disorders Diagnosed (Ref: No)			
ADHD	2.589	2.010-3.334	<0.001
Bipolar Disorder(s)	2.746	2.131-3.539	<0.001
Depression	1.343	1.026-1.758	0.032

Anxiety	1.338	1.020-1.755	0.036
Learning Disorder(s)	0.788	0.587-1.057	0.112
Adjustment Disorder(s)	0.750	0.564-0.996	0.047
Conduct Disorder	1.025	0.778-1.352	0.859
Oppositional Defiant Disorder	1.173	0.893-1.540	0.251
Schizophrenia	1.035	0.712-1.504	0.859
ER-visit/hospitalization	1.020	0.834-1.248	0.844

Table M3. 4 Multilevel Logistic Regression model to determine the association between structural equivalence exposure and psychotropic polypharmacy

Characteristic	OR	95% CI	p
PRACTICE CHARACTERISTICS			
Practice Size	0.999	0.968-1.030	0.944
Type of Practice (Ref: Primary Care only)			
Specialists only	1.690	0.854-3.345	0.132
Mix	1.040	0.578-1.874	0.895
Others only	0.653	0.223-1.911	0.436
PHYSICIAN CHARACTERISTICS			
Structural Equivalence Exposure	4.236	2.071-8.666	<0.001
Specialty (Ref: Primary Care)			
Specialist	3.532	2.113-5.904	<0.001
Others	1.329	0.682-2.591	0.403
Physician Gender (Ref: Female)			
Male	1.221	0.981-1.521	0.074
PATIENT CHARACTERISTICS			
Patient age	0.997	0.979-1.016	0.751
Number of mental/behavioral disorders diagnosed	1.066	0.885-1.285	0.500
Patient Gender (Ref: Female)			
Male	1.148	1.007-1.308	0.039
Patient Race (Ref: African American)			
Alaskan/American Indian	1.537	0.483-4.887	0.467
Asian/pacific	0.305	0.134-0.696	0.005
Caucasian	1.634	1.391-1.920	<0.001
Hispanic	0.745	0.632-0.878	<0.001
No ethnicity	1.392	0.931-2.082	0.107
Mental/behavioral Disorders Diagnosed (Ref: No)			
ADHD	2.556	1.984-3.292	<0.001
Bipolar Disorder(s)	2.743	2.128-3.536	<0.001
Depression	1.346	1.028-1.763	0.031

Anxiety	1.338	1.019-1.755	0.036
Learning Disorder(s)	0.786	0.585-1.055	0.109
Adjustment Disorder(s)	0.748	0.563-0.994	0.045
Conduct Disorder	1.028	0.779-1.355	0.847
Oppositional Defiant Disorder	1.171	0.892-1.538	0.255
Schizophrenia	1.045	0.719-1.519	0.816
ER-visit/hospitalization	1.019	0.833-1.246	0.857